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ACTA PÆDIATRICA SCANDINAVICA

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A 10-year Prospective Follow-up Study of 2268 Cases at the Child Guidance Clinics in Stockholm

Edited by HANS CURMAN and INGVAR NYLANDER

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The Child Psychiatric Department of Karolinska Institutet
at St Göran Hospital, Stockholm, Sweden
(Head, Professor Ingvar Nylander)

A 10-YEAR PROSPECTIVE FOLLOW-UP STUDY OF 2268 CASES AT THE CHILD GUIDANCE CLINICS IN STOCKHOLM

by

Hans Curman and Ingvar Nylander

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CHAPTER 1 INTRODUCTION AND LITERATURE SURVEY

Introduction

In his publication entitled "The state of the art and science in child psychiatry" (1973), Anthony develops a number of critical arguments on the subject of child psychiatry. In our daily work we are involved in a multitude of diversified tasks which completely absorb our energies. How can we find time for education and research? The depth of involvement and the refinement of therapy is indeed impressive, but if one were to ask the child psychiatrist and his assistents for an account of methodological tests or research projects, we should be treated to an embarrassed mumbling about time and outside pressures. In Anthony's opinion, there is reason to be perturbed about the future of child psychiatry as a scientific subject — "... the art has flourished but the science has stood still" and he maintains that "... we need to become accustomed to the process of conjecture and thereby to establish predictive skills". If we desire to take part in the scientific discussion and to develop our discipline, we must also acquire greater knowledge and better controlled base material for our evaluations than we possess at the present time. We must contribute as much time to the research as we give to the "art".

This book is an attempt to examine, using scientific methods, a fragment of work taken from a great many years of medical practice devoted to child psychiatry. In the debate in question, it has been queried whether there is any justification for trying to measure, by various means, the effects of psychiatric–psychological treatment. Information as to whether the patient will require further psychiatric care after his treatment has been completed or whether he will revert to his former transgressive behaviour, or commit asocial offences or conform to normal patterns, does not provide us with a satisfactory measure of the efficacy of the treatment method. At the same time it has been maintained that committing a patient to a psychiatric clinic, a home for alcoholics or a prison, will create new problems for the patient even though he will be receiving a certain amount of help. One such problem will arise as a result of alienation processes. The patient is declared to be a sick person, or an alcoholic or a criminal. His confidence is undermined and his possibilities of obtaining employment and establishing contact with others is diminished. Clearly, the prevention of such a trend must be acknowledged as a meaningful task. However, in order to be able to accomplish this, it is necessary to possess data pertaining to the individuals who, in the years to come, run the risk of becoming members of the clientele handled by the psychiatric clinics, the temperance authorities or the police. The child psychiatrist should be in a position to make several important contributions.

Even though we may be aware that no causal relationships exist between simple quantitative data on the one hand, and mental diseases or asociality on the other, we nevertheless feel that any answers that can be found for the following questions are definitely pertinent.

1. What will happen to our patients in the coming years? How many of them will be in need of continued psychiatric care after being discharged from the CGC? How many will be in need of supportive measures from the community? How many will, in time, be in contact

Abbreviations and comprehensive terms

CGC – Child Guidance Clinics

Mental register – Persons registered as patients at the CGC or at child psychiatric or psychiatric clinics and departments or at local Mental Health Units

Asociality register – Registers maintained by the Social Welfare Board (on children and young people known for asocial behaviour), by the National Board of Excise, by the Temperance Board and by Criminal Offences

with alcohol polyclinics and law enforcement authorities?

2. Is it possible to predict, on the basis of the investigation technique and the working methods that are used daily in child psychiatric care and from the information given by these procedures, which of our patients are likely to be in need of medical or social care facilities.

In the following report we shall discuss what has happened to our patients in these respects during the first 10 years after being discharged. A further report is in progress in which the results of a 20-year follow-up study will be presented.

Literature survey

What happens to the children and young people who seek help for nervous symptoms and behaviour disorders when they grow older?

These aspects have been studied in Sweden by ...cander (1950) who followed up 308 children, who had been examined and treated during the years 1938–43 at the Erica Foundation (Ericastiftelsen in Stockholm). After an observation period of 1–10 years, 51 were found to be free from symptoms, 34 % were improved, while 15 % remained unchanged. The study does not state whether this latter group had applied for aid for nervous symptoms or for developed asociality during the observation period.

Reinius (1956) interviewed the parents of children who applied for aid at a child guidance clinic in a Stockholm suburb in 1952. The number of cases totalled 120 and the observation period covered about 2 years. 87 of the patients were stated to be improved, 10 were unchanged and 3 had deteriorated.

Dahl (1965) followed up 138 cases who had been under hospital care at a child psychiatric department in Copenhagen, with an observation time of 6–8 years. In about 78 % of the cases, the children had developed to become socially well-adjusted or reasonably well-adjusted, while the remaining cases showed definite adjustment problems. The children showing the best results had come from intact homes and had been living under secure social circumstances, which also applied to the children exhibiting a neurotic picture during their stay in hospital. The children who were considered to be psychotic or who showed behavioural disorders during their hospital visit were accorded a poor prognosis. The boys over the age of 10 years who had been charged with pilfering were given a very poor prognosis.

Robins (1966) has presented a retrospective follow up study of 524 normally talented children under the age of 18 years who had been in contact with a child guidance clinic in Baltimore USA. The study covered an observation period of 30 years. As control material, Robins selected a group of 100 cases, taken at random from the same school register as the patients. All the cases were investigated thoroughly. The primary material has not been described in detail because the journals available were far from complete but in about 70 % of the cases the patients had been referred to the clinic on the grounds of asocial symptoms. In the follow-up study it was found that 45 of the patients and 4 % of the control subjects showed 5 or more symptoms of antisocial behaviour. Only 20 of the patients had not required help for mental trouble during the observation period, while the figure for the control subjects was 52 %. In the follow-up study 34 % of the patients and 8 of the control subjects were considered to be suffering from serious mental symptoms. The more serious the symptoms of asociality in the teenager the severer the degree of mental disturbance in the adult. On the other hand the children who at the primary examination needed help for symptoms of neurotic states were found later to resemble the control group with respect to their subsequent adjustment. Symptoms of shyness, reticence, nervousness, irritability, tantrums, fear, speech defects, oversensitiveness and difficulties in falling asleep and also tics, had no relationship with the mental health picture exhibited in later years.

Sundby & Kreyberg (1968) performed a detailed follow-up study of 277 patients (173 boys and 104 girls) who had been cared for at a child psychiatric department in Oslo during the years

1950–54 The observation time covered 11–15 years. The symptomatic picture for this clientele was very mixed, 45 % being regarded as neurotics, 15 % as psychotics, 10 % as personality disturbances, and 30 % as retarded. The results of the follow up study showed that the neurotic group had overcome their difficulties better than the other two groups 80 % fully recovered or showing only mild symptoms, as opposed to 7 % and 39 %, respectively Factors regarded as contributing to an unfavourable prognosis were incomplete families, homes with emotionally disturbed parents, symptoms manifested during hospitalization such as difficulties in making and maintaining contact hyperactivity passiveness and antisocial behaviour

King & Pittman (1969) followed up 65 young people between the ages of 12–19 years who had been consecutively hospitalized for acute care at psychiatric clinics. The observation period covered 6 years. The prognosis was poorest for those who during the hospitalization period, were diagnosed as suffering from psycho-somatic syndromes, schizophrenia, hysteria and sociopathy with symptoms persisting in 77 % of the cases, while 79 % of those who were diagnosed as neurotic did not exhibit any symptoms at all at the conclusion of the observation period.

A highly commendable summary by Rutter (1972) presents material that documents the relationship between mental disturbances in childhood and in adulthood. With respect to the schizophrenic psychoses, Rutter expresses his opinion that there is ample documentation for discounting the existence of any relationship between schizophrenia and infantile autism.

Furthermore, no relationship has been proved to exist between the psychoses that first appear in early childhood and those that make their debut later (quotation from Kolvin 1971). The latter type resembles to a large degree the forms that make their debut during the adult years. Kolvin draws the conclusion that schizophrenia can make its debut with psychotic symptoms during the latter years of childhood but that these schizophrenic symptoms seldom appear before the age of 7 or 8 years. However other opinions (quotation from Lane & Albee 1965 1966, Frazer 1953 Bower et al. 1960, etc.) maintain that people who succumb to schizophrenia as adults often showed symptoms during childhood of poor adjustment to school, unsatisfactory relationships, and peculiarities of behaviour as well as stating that schizophrenia appears to be frequently preceded by prepsychotic abnormalities during childhood.

With regard to neuroses, Rutter makes the comment that it was previously assumed that there was a state of continuity between childhood neuroses and the neuroses of adulthood but that more recent studies queried the validity of this assumption. The studies cited by Rutter include one by Robins from 1966 in which the author reports that neuroses in adulthood were not more common among those who had needed child psychiatric care than for the control group The majority of those who had been neurotic as children were not neurotic when they became adults. However Rutter does not feel that any definite conclusion can be drawn from these results. Nevertheless, there are other investigations (quote Michael et al 1957 Robins, 1971) that present similar postulations. Rutter summarizes by saying that there is some degree of continuity between child neuroses and adult neuroses but that this continuity applies only to a small proportion of each group. Most neurotic children grow up to be healthy individuals and the majority of neurotic adults acquire their neuroses during their adult years.

Referring to "neurotic characteristics" in childhood (thumb-sucking, nail-biting, stammering, bed wetting, etc.), Rutter is of the opinion that there is no evidence to prove that these characteristics represent neuroses, either in childhood or in adulthood.

According to the experiences gained from adult psychiatry affective diseases are seldom diagnosed in children before the age of puberty Manodepressive states are practically unknown in childhood (quote Anthony & Scott 1962) and neurotic depressions are seldom diagnosed before puberty However child psychiatrists have reported that depressions are not an uncommon

Wernstedt and Dr Gideon Nordahl, who was both teacher and doctor—had been engaged in running a counselling service a few evenings a week with the help of voluntary unpaid assistents. Ordinarily the doctors were attached to the staff of the pediatric hospital, Allmänna Barnhuset Norrtulls Hospital.

Finally inspiration came from the Continent and from the USA where admirable progress was being made in the field of mental hygiene. The outstanding man in this field in Sweden was Viktor Wigert, Professor of Psychiatry who took the initiative in founding a mental hygiene association in 1931—The Swedish Association for Mental Health—and later petitioned Alderman Oskar Larsson to set up a child guidance clinic in Stockholm. Wigert also supported the clinic during the first years of its existence by serving as its Inspector

The Child Guidance Clinic (CGC) in Stock m thus became the first official body in Sweden handle the mental care problems of children nd young people. The work of this institution has continued without interruption through the years, and is now being run under the auspices of the Child Guidance Clinics of the Stockholm County Council.

The experience of this institution later came to be used as a basis for the proposal laid forth by the Child and Adolescent Mental Welfare Committee of 1944 for organizing state-supported child guidance clinics in the various counties of Sweden. The Youth Guidance Committee was an offshoot of the Department of Justice and the proposed organization was designed with a view to outpatient care where childpsychiatrists, psychologists and psychiatric social workers participated as a team in attempting to prevent social maladjustment and criminality in children and youth people up to the age of 21 years. The clinics were intended to satisfy the need for counselling on the upbringing of children and to supply treatment for cases of maladjustment, deviating mental development or intellectual retardation in children and young people Emphasis was placed on the preventative nature of the work. Although the activities were predominantly run on an outpatient basis, a few beds were to be available at children's wards in hospitals for cases who needed further observation.

When the Mental Health Delegation of 1957 and 1958 a Home Office subcommittee of enquiry presented its resolutions I and II concerning child guidance clinics, treatment centres and mental hospitals for children and young people the main emphasis was quite naturally placed on hospital care aspects, the aim being chiefly to supply the necessary medical and psychiatric facilities for children suffering from mental disorders

At the same time, it was stated plainly that the greater part of the activities in the larger towns and cities should obviously be designed as comprehensive outpatient care facilities and that the lines of development that had been followed in Stockholm were fully acceptable

It can be seen from the aforegoing that the two official reports upon which the expansion of the original child guidance clinics was based, supplement each other on several important points

The first report was chiefly concerned with preventative and social aspects, while the second report dealt primarily with medical and health care problems

As both viewpoints are clearly equally important the basic motives behind these two reports should be borne in mind when pursuing the subsequent developments that occurred in the State run child and youth guidance clinics.

Thus, CGC in Stockholm was administered from the initiation in 1933 by the Child Welfare Board. The organization has consistently been under pressure to furnish a child psychiatric service for the children's social welfare offices, and also to design the work with a view to prophylactic measures and to meet the needs of the public—these latter aspects being of primary importance The conditions governing the running of the work at the present time are derived from this double burden of pressure

It became obvious at an early stage that the considerable variety of tasks which the clinics were faced with, had to be dealt with on a differential basis. Routine procedures had to be modi-

fied and adjusted. For example, it was not possible to maintain contact with the young asocial clientele at fixed times, like the regular appointment times followed when working with ordinary members of the public who needed assistance A doctor was therefore appointed (this step was taken relatively early in 1951) to be available according to a more flexible time table. His position was given the title of Social Welfare Medical Officer In practice, his place of work was in the immediate vicinity of the premises occupied by the Child Welfare Services, where he remained when the organization transferred various other facilities to different districts in the Stockholm area.

The clientele requiring help increased in volume over the years and applied to the CGC offices that were set up in different parts of the city This expansion corresponded to the increasing demands made by the children s social welfare centres on the services of the available CGC The burden of work of the Social Welfare Medical Officer doubled but did not leave sufficient time for acute situations, necessitating visits, arising at the homes for children and young people In line with the increasing concentration on therapeutic measures, it was considered to be essential to help the children and young people who had had to be placed in institutions by cooperating even more closely with those in charge of them, the personnel at these institutions. This, too, required reinforced resources and new procedures, e g. discussions—individual or groupwise—with both personnel and clientele A task of such proportions could not be undertaken unless personnel was made available for these important new activities, which meant doctors, psychologists and psychiatric social workers. So, in this manner the guidance clinics were successively built up, those attached to Children s Homes being established in 1955 while those attached to the Homes for Young People being started in 1959

In dealing with problematic children of school age and the upper teens, the welfare teams found that, time and again, the origin of the mental disturbances could be traced back to the child s early years. This finding prompted the initiation of organized collaborative efforts between CGC and the Well-Baby Clinics (1953), and, later (1963) also between day care centres and play schools.

This joint work required special personnel and new working procedures. In their contacts with the Well-Baby Clinics, the psychologists and psychiatric social workers concentrated on interesting the staff—nurses and paediatricians—in problems associated with mental hygiene In addition to their normal work of physical control examinations. By developing this interest, the staff could then become helpful in tracing children who are in need of help and arranging for their contact with CGC where they can be taken in charge for diagnosis and treatment. A few years ago a programme of medical control of all 4-year-olds was introduced, as a result of which the mental hygiene activities of the Well-Baby Clinics have been expanded to cover a number of very important, additional duties. Even in the case of the children s day care centres, efforts have been made to enlist the interest of the personnel. A group consisting of psychologists and psychiatric social workers attached to the Child Guidance Clinics maintains constant contact with the centres as visiting consultants on matters of mental hygiene.

A concentration on the important pre-school years implies also the setting up of special small day care centres with a programme of therapeutic activities connected with the guidance clinics, and special centres for children with grave mental disturbances that are also run within the framework of the organization. These day centres serve two purposes the children are under constant observation and they receive therapy which is a combination of medical and pedagogical treatment. The first of these therapy day centres was started in 1953 and was housed in a building separate from the CGC. Since that time, the centres of this kind set up in Stockholm have always been a part of the child guidance clinic premises, which is advantageous for concentrating the work involved with this category of men

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tally disturbed pre-school children and their families.

In order to be able to follow through treatment of children with certain types of deviations, who would otherwise most probably have to be taken from their homes and placed in institutions, therapy schools have been set up which provide special classes and where the recreation periods are organized to provide activities designed to improve mental health. The children attending these schools are selected as a result of collaboration with the personnel of the various child guidance clinics.

Active therapeutic contributions are also made by the therapeutic summer camps arranged each year and run with the aid of staff employed by the Child Guidance Clinics.

Individual therapy and group therapy with children and with parents, has been an essential part of the activities programme, with a successive shift of emphasis towards treating the family as a unit.

The preventative measures adopted by the Child Guidance Clinics are based on an understanding of the child's development and requirements at different ages, and on experiences gained from therapeutic treatment. In this work, the target groups are expectant parents, personnel and parents at the Pre natal and Well-Baby Clinics, at day care centres, at schools, etc.

To a large extent, the activities run by the Child Guidance Clinics involve a confrontation between social work and the theory and practice of child psychiatry. In this respect confrontation is a fruitful process, leading to progressive developments in both fields.

The purpose underlying the development and expanded organization of the Child Guidance Clinics is to fulfill, to the greatest possible extent, the demands made upon the CGC-facilities by society. These demands are many and can be exemplified as follows:

- demands of the general public for help
- support and treatment of different kinds
- demands made by official homes for children and youths for assistance with observation measures and therapy planning, various types of treatment, and instructions for personnel
- demands made by the social services for assistance in particular cases, and assistance in the form of consultants and counsellors
- demands made by the health services for an outpatient care in connection with child and youth psychiatric organization
- demands made by the schools for a complement to the pupils' counselling services, and for assistance with facilities for children with special school problems
- demands for active contributions in preventative social work and health services
- demands for special measures for particular risk groups, mentally handicapped children, socially deprived families, home environments disturbed by alcoholism, and so forth.

Basic psychological–sociological aspects

The basic pattern of personality development follows certain rules that are common for all people. Starting from constitutionally determined limits, the individual pursues successive development phases from birth until old age. The newly born child enters into a state of interaction between himself and his environment which, to start with, is represented only by his mother (or mother-substitute) but which later widens to include his father, siblings, friends and an increasing number of other people and relationships. The way in which the environment responds to the child is of importance to the way in which the child develops a grasp on himself, on other people and on his own position in relation to others. These are experiences and relationship patterns which are initially confined within the limits of the family and in which the family members function by interplay. In a broadened perspective it becomes clear that the social configuration of the family is an important factor in the insight experienced by the individual members of the family into the individual situation and into the individual's relationship with other people and is thus also a decisive factor in personality development.

The manner in which the child is accepted

affects its development as a person, and also affects the child's own acceptance of others. Security and demand fulfillment during childhood is of vital importance The child needs the help of adults who are themselves more or less secure in order to solve conflicts between his own impulses and the demands of reality This provides him with a foundation for his own initiative and for testing new roles that will further his maturity processes Small children do not possess the perspective that is necessary for correcting earlier experiences in the light of later experiences. The flavour left by earlier situations therefore persists when new ones arise and require interpretation, and the pattern thus formed will replicate into the adult years. Conflicts and deficiencies in the relationship between the child and its environment can become manifested as behavioural disturbances or neurotic symptoms, which can be regarded as a sign that there is something in the interplay between the family members which is not functioning as it should. The child's problems will in turn affect the response he elicits from his environment. The worst situation that can arise is when the child receives further confirmation that he is not accepted, which will lead to a reinforcement and consolidation of the original problematic structure and, possibly new and intensified symptoms. In later years, when these children become parents, they will respond to their own children in the same (or the absolute opposite) way this being the only way of which they have any emotional experience Thus, we see how often problems are carried over from one generation to the next. And this is the reason why it is so important to work with the whole family surrounding the disturbed child. As the family is regarded as the basic unit for the ability of the individual to relate to other people the therapeutic measures must of necessity be focused on family relationships.

It can be said that mental and social problems can be viewed on different levels.

The intramental level embraces the total mass of experience and behaviour patterns contained within and exhibited by the individual.

The inter-personal level describes and clarifies the interplay between a smaller number of individuals who are assumed to maintain relatively stable relationships with each other The family is a good example of a group that can function in different ways. The interplay between family members represents a fertile object for analysis, leading to a greater understanding of relationship patterns which, when found to be unsatisfactory can then be altered.

The structural level covers all the relationships held by individuals and by groups in relation to society as a whole The social and economic status of a family affects the family members picture of society and their relations with society's institutions and social features, such as day homes, schools, the labour market, housing conditions, and so on.

Problematic areas—target groups

The Child Guidance Clinics are open for families with children between the ages of 0–20 years. There is a marked dominance of boys of preschool age and, even more so of school age. In the age group 15–20 years, the girls are slightly more dominant The number of pre-school children and of teenagers differs somewhat depending upon the district in which the clinic is situated whether the district is an old community or a new one Generally speaking, the total number of youngsters has increased continuously

The problems vary from simple "behavioural disturbances" obstinacy and stubbornness, temporary anxiety states to more serious deviations of a psychopathological and antisocial nature.

The primary target group for the work of the CGC comprises children, young people and their families, where there are individual difficulties or problematic relationships within the family or in relation to other individuals or groups that are included in the environment. Everyone who requires help for problems of this kind can turn to the CGC and receive qualified assistance from trained personnel.

Apart from this basic group of families, who contact the CGC more or less on their own initia

tive there is another large group that has been referred to the CGC by other social authorities. As mentioned earlier the CGC has established routes for collaboration with the Well Baby Clinics and the day care centres and nursery schools, where efforts are made to detect problems at an early stage and to prevent problems arising. In these instances, attention is directed towards collaboration with both personnel and parents. The schools also mediate in contacting the CGC—either direct or through the team of pupil's counsellors—when a child's problems result in situations that cannot be dealt with within the framework of the school's facilities. The Children's Social Welfare Organization in Stockholm has always maintained a very well organized system of cooperation with the CGC.

Current arguments tend to differentiate between social and mental disturbances. This implies a risk of oversimplification and standpoints are inclined to be too static. Social and mental problems should be regarded more as different means of expressing dissatisfaction with a situation as it is experienced by the individual or the group (the family). Problems that are strictly social or strictly mental are therefore not feasible One aspect may predominate but the other aspect is always present

In the families who contact the CGC, the main weight of the problem complex can be placed either on the psychiatric or on the social aspects. There are families whose problems are expressed chiefly in psychological terms in the form of symptoms exhibited by a single family member and/or disturbed relationships within the family In other families, one member (most frequently a child) shows social deviations while the rest of the family is free from such symptoms. Finally there are some families whose difficulties are clearly defined as social disturbances, i.e. conflicts in relation to society

Social and ps[illegible]ch[illegible]l[illegible]gical difficulties have a tendency to inten[illegible]f[illegible] each [illegible]ther so that the families with the greatest burden of social problems are often [illegible]fli[illegible]ted [illegible]th equally heavy psychological comp[illegible]x[illegible] [illegible] families live under such difficu[illegible] cir[illegible] [illegible] is fully motivated to devote a proportionally large part of the CGC treatment and therapy resources to helping such families.

Methods of work

Even though it is the child or the teenager who manifests the symptoms, it is always the family as a whole that must be the focus for the work of the CGC In order to understand the child's difficulties and reactions, it is necessary to gain insight into the child's relationships with his family and the individual members. If we are to help the child, we must be able to help the family as well as understanding the family's position in relation to society The child's inner conflicts and, in case of sickness, his physical health, the parents personal problems, tensions and strains between the parents and between family members, sibling rivalry and other sibling conflicts, are all part of family dynamics, which constitutes the field of work. But in order to continue working with the family there must be a basis consisting of the positive resources that can be activated within the family in each single individual. The statistics given for the number of children and their symptoms are therefore misleading insofar as a considerable amount of work is expended on family members who are not recorded on registers and on a great variety of family problems, quite apart from the actual child in question The family's housing conditions, the immediate neighbourhood and the surrounding district—the child's day home, school friends and associates and his relations with these, youth centres—these are all important factors, as are also the parents conditions of employment, relationships with relatives, neighbours and friends, state of health, and so forth The total picture is thus many-facetted and includes social, psychological, pedagogical and medical factors that must be studied and worked upon. In order to deal with this complicated task, the CGC has developed its scope in close cooperation with professional groups whose field of work is necessary to the work of the CGC doctors, psychologists, psychiatric social workers, teachers, and administrative personnel. Thus,

a team usually consists of a doctor two psychologists, three social workers and two secretaries.

The treatment of mental problems is based on the assumption that the basic pattern of personality development as described earlier is known in detail It also assumes an insight into the factors that can stimulate the development of personality characteristics that prevent an individual from realizing his capabilities with respect to fulfilling his emotional requirements and entering into a mutual exchange of relationships with others.

It is important to be able to analyze the problem complex in view of the fact that the origins of the problems have their roots chiefly in experiences far back in the past which have been overlayered successively ever since Or alternatively the problems may be of recent origin—a direct reaction to a current situation. The background is thus clarified by the analysis.

In the first instance the therapy is designed to help the individual (child, teenager parent) to understand himself and his reactions in the light of previous experiences. This offers a possibility of actively participating in building up satisfactory relationships and situations, as well as helping the individual to experience himself and other people in a new and more satisfying way The individual is given the opportunity of repairing a personality development that went wrong and of substantiating a large portion of his personal capabilities. Frequently this involves working directly with the familial problem complex that has grown up around the family members. The aim is to pave the way for new grounds where the family members can meet, and which allow for improvements towards conditions of family life that are more satisfactory for all parties.

In the second instance i.e when the disturbances result from a current crisis, the actual problem complex may be more or less deep. However the focus of the therapy is on the crisis itself This type of acute or short term therapy often requires the same amount of knowledge and experience as treatment which must be followed through over a long period of time.

The two types of problem complexes described above are extremes that hardly ever occur as completely separate and unconnected manifestations. In judging the situation, it is important to include both aspects and to consider how they are related to each other

In many cases, the problems may be rooted in disturbed familial relationships. This often implies conflicts and unresolved misunderstandings between the parents and one or more of the children. Therapy is then focused on the relationships themselves, and takes the form of mutual participation talks, family therapy or at-home therapy

In some families, the nature of the mental damage is such that the prospects for psychotherapeutic measures are negligible. But, by maintaining contact with the CGC over a period of years, during which time the CGC constitutes a security factor to be relied on through various crises, these families can nevertheless hold together and manage to cope without needing institutional care

Alternative treatments

The form of application for help can vary according to the CGC receiving the request, but all the clinics strive to shorten the waiting time and arrange for a first meeting between the family and the representative for the clinic as quickly as possible. As a rule this meeting takes place within 14 days of the application being received. Acute cases, such as young people who telephone themselves and ask for help, are very often given immediate priority and an appointment is arranged for the same day

Sometimes home visits are made when the application has been received, in order to prepare, smoothly and quickly the contact with the entire family

Once the first contact has been made each case is taken up and discussed at an internal conference attended by all the members of the team In quite a number of cases, this first consultation, possibly in combination with some other outside aid measure or by referring the case to another authority was all the help that was

tive, there is another large group that has been referred to the CGC by other social authorities. As mentioned earlier the CGC has established routes for collaboration with the Well-Baby Clinics and the day care centres and nursery schools, where efforts are made to detect problems at an early stage and to prevent problems arising. In these instances, attention is directed towards collaboration with both personnel and parents. The schools also mediate in contacting the CGC—either direct or through the team of pupil's counsellors—when a child's problems result in situations that cannot be dealt with within the framework of the school's facilities. The Children's Social Welfare Organization in Stockholm has always maintained a very well-organized system of cooperation with the CGC.

Current arguments tend to differentiate between social and mental disturbances. This implies a risk of oversimplification and standpoints that are inclined to be too static. Social and mental problems should be regarded more as different means of expressing dissatisfaction with a situation as it is experienced by the individual or the group (the family) Problems that are strictly social or strictly mental are therefore not feasible. One aspect may predominate but the other aspect is always present.

In the families who contact the CGC, the main weight of the problem complex can be placed either on the psychiatric or on the social aspects. There are families whose problems are expressed chiefly in psychological terms in the form of symptoms exhibited by a single family member and/or disturbed relationships within the family In other families, one member (most frequently a child) shows social deviations while the rest of the family is free from such symptoms. Finally there are some families whose difficulties are clearly defined as social disturbances, i.e. conflicts in relation to society

Social and psychological difficulties have a tendency to intensify each other so that the families with the greatest burden of social problems are often afflicted with equally heavy psychological complexities. As these families live under such difficult circumstances, it is fully motivated to devote a proportionally large part of the CGC treatment and therapy resources to helping such families.

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Even though it is the child or the teenager who manifests the symptoms, it is always the family as a whole that must be the focus for the work of the CGC. In order to understand the child's difficulties and reactions, it is necessary to gain insight into the child's relationships with his family and the individual members. If we are to help the child, we must be able to help the family as well as understanding the family's position in relation to society The child's inner conflicts and, in case of sickness, his physical health, the parents personal problems, tensions and strains between the parents and between family members, sibling rivalry and other sibling conflicts, are all part of family dynamics, which constitutes the field of work. But in order to continue working with the family there must be a basis consisting of the positive resources that can be activated within the family in each single individual. The statistics given for the number of children and their symptoms are therefore misleading insofar as a considerable amount of work is expended on family members who are not recorded on registers and on a great variety of family problems, quite apart from the actual child in question. The family's housing conditions, the immediate neighbourhood and the surrounding district—the child's day home, school, friends and associates and his relations with these, youth centres—these are all important factors, as are also the parents conditions of employment, relationships with relatives, neighbours and friends, state of health, and so forth. The total picture is thus many-facetted and includes social, psychological, pedagogical and medical factors that must be studied and worked upon. In order to deal with this complicated task, the CGC has developed its scope in close cooperation with professional groups whose field of work is necessary to the work of the CGC. doctors, psychologists, psychiatric social workers, teachers, and administrative personnel. Thus,

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In numerous cases ambulant therapy is inadequate and various forms of environmental therapy must also be included in the programme In the case of the younger children, there are therapeutic nursery schools and day care centres serving this purpose that are available for children with environment-dependent emotional disturbances. Many of the guidance centres are organized to include therapeutic sections housed on the centre premises, which is a great advantage for team collaboration during the handling of a family project.

For children with brain damage and other marked deviations of diffuse etiology there are a couple of special small therapeutic day care centres where the children are put into observation and therapy groups.

Further for the children of school age there are a couple of small therapeutic schools that can be defined rather as external therapy day centres, each taking about 14 children and organized to provide schooling and recreational activities. The form of schooling constitutes the framework for the mode of therapy which is thus centered on and around the school activities. The pedagogical work is combined with different forms of psychotherapy both individual and groupwise. Apart from these facilities for taking care of the children, very extensive efforts are made to influence the familial problem complex. This is achieved either by direct treatment of the parents or by unconventional contacts between the families and the personnel, such as arranging activity evenings each week in which everybody including the pupil s siblings, participates.

Another form of environmental therapy is organized during the summer months at the summer colonies and camps arranged by the CGC out in the Stockholm archipelago and further north in the county of Jämtland The summer arrangements are an important part of the therapeutic programme run by the CGC Small groups of children 8–15 in number between the ages of 8–13 years (current age distribution) are accepted at the colonies and camps for a period of just over a month. The personnel is comprised mainly of persons employed at one or other section of the CGC organization Since the entire personnel is involved in the therapeutic aspects of the visit the therapeutic environment is homogenous and the therapy itself is intensive and systematic

Over and above the resources for therapy already mentioned and which are directly associated with the guidance centres, the CGC is granted an official allowance that can be used to finance psychotherapy for parents and young people who are considered to be suitable subjects for psychotherapeutic treatment outside the scope covered by the CGC activities. The allowance can also be used to defray fees for group and family therapists employed on a temporary basis and for pedagogic leaders in charge of activity groups. All counselling and treatment within the framework of CGC is free of charge.

With the backing of the therapeutic resources described above, it is possible to enter into discussions regarding suitable plans for treatment, for and in consultation with families requiring help Upon occasion some of the therapy forms can be used in combination at other times, the trial-and-error method is applied until the most suitable mode of therapy is found. The results of the facilities offered are evaluated in the first instance, by the families themselves and by the therapy team, although a check on the effects is also kept by maintaining regular contact with day homes, schools, etc. providing the parents give their approval to this procedure.

Community work

The work of the CGC can be divided into two main categories

- aid given direct to the general public
- participation in various aspects of community work.

On the basis of the experiences gained from projects designed to help families achieve a solution to their various difficulties, the CGC also extends its activities into a much wider field where the contributions called for involve visiting and preventative measures. This type of work is

focused on groups such as expectant parents, personnel at the pre-natal clinics, the day homes, the schools, etc., and the trainee personnel working in these institutions.

For the past two or three years, the members of the teams employed at the CGC-run centres also act as consultants to the Homes for children and young people that are situated in the districts covered by the regional CGC organizations. This contribution has had an impact on the development of the forms for institutional care towards a greater emphasis on therapeutic measures and has led to a very lively interest in further training by the personnel at these institutions.

As well as these activities, the teams from the guidance centres work on a regular and continuous basis in association with the technical staff in adjacent fields such as the schools, the Child Welfare Board, and other types of institutions for children and young people The design of this associative work is such that the CGC personnel serve as counsellors for teachers, for the day home personnel and the youth centre staff for social welfare workers, etc., furnishing them with support and advice with respect to their work with severely mentally disturbed children and youngsters.

A CGC-personnel group consisting of psychologists and psychiatric social workers serves as a team of consultants to the Well-Baby Clinics, where their activities include running advanced courses in mental hygiene for the regular Clinic staff This extended training is arranged largely in the form of staff meetings, discussion groups which are attended by parents and deal with problems relating to children and upbringing, private consultations with families with small children, which may take place either at the family home or at the Clinic, and so forth.

The consultants function concurrently as liaison officers between the Well-Baby Clinics and the Child Guidance Clinics, and can refer children and families for examinations or continued treatment to the various guidance centres if such a move is considered to be necessary Another section of the work is concerned with liasons between other help-giving authorities in the community The health control programme for 4-year olds recently introduced by the National Social Welfare Board represents a very important addition to the work of the consultant team, whose task it is to follow up the mental hygiene and developmental-psychological aspects of the programme

The future plan is to expand the activities and to distribute the resources so that consultants can be attached to each CGC-centre and with regular duties at all the Well-Baby Clinics within the region covered by the CGC-centres.

There is also to be a group of psychologists and psychiatric social workers employed by the CGC who are to serve as consultants to the children s day care centres and nursery schools, their task being to take care of mental-hygiene aspects of the work on an ambulatory basis.

Children with deviating behaviour are reported to the consultants directly by the personnel of the day care centres. The consultants will then proceed to investigate the child's circumstances and, in cooperation with the day care centres personnel and the child's parents, attempt to reach a solution to the problem.

Despite this collaboration, there are always some cases with problems so complex that it must be the task of the team to negotiate the best possible contacts with other authorities, such as the CGC-centre, the Child Welfare Committee or a suitable hospital.

A very important part of the work of the team are the activities involving personnel groups.

In connection with the current expansion of day care centres, the consultation function of the teams has been put to use in planning the new premises and also in planning various trial activities in new housing projects.

Cooperation with the schools during the transition period when the children first become acquainted with their school and its routines is also a very important part of the work.

Unfortunately the funds available for the work, particularly consultant work, are very far from adequate.

Activities during the initial years

The work of the CGC has been directed at the family as a unit right from the very beginning.

The first unit of CGC opened on a very modest scale in 1933 with a staff consisting of two full-time employed social workers and a part time psychiatrist The social workers were Carin Colliander with a degree in sociology and mental hygiene training at Smith s College for Social Work in the USA, and who was later to become the Head of the Family Guidance Bureau in Stockholm, and Edith Wennerberg, M.A., who had considerable experience of work with children from Homes for children and young people. Dr Rikard Eeg-Olofsson, the psychiatrist was the first doctor on the scene and he too had experience of the work of the children s homes as well as being experienced in psychotherapeutic work with adult clientele. The doctor was also given the appointment of Medical Officer for Remedial Classes in Elementary Schools (Folkskolor).

After one year Dr Eeg-Olofsson was replaced by Dr Torsten Ramer the psychiatrist and neurologist, who subsequently became Head of the CGC until 1948, when he was succeeded by the present author (Hans Curman) Dr Ramer also served concurrently as Medical Officer for Remedial Classes and upon relinquishing his appointment as Head of the CGC, devoted his efforts entirely to the schools.

The role played by the psychiatric social workers was central and independent. Conferences were held at least once a week with the doctor present as an active participant, and practically all the cases to be dealt with were the subject of mutual discussions. The topics brought up included the training of parents and guardians, the importance of regular home visits with the approval of the parents—and the team received criticism for trying to avoid, as far as possible, placing children in institutions. The behaviour of the children was interpreted as a reaction to their environment. The idea of psychotherapy in some form for the children was present from the start, but it was not possible to give it a practical shape because of the inadequacy of the resources and the available personnel

Already during the first year the CGC took the initiative in starting an "observation" class, which—as was, in fact remarked upon at the time—should have been called a "therapy" class. The children were selected and followed up by the CGC.

In 1934 the CGC organized a summer colony which was also intended to provide therapy for the clientele, with the resources orientated in this direction. At this time, collaborative work was started with the "play room" set up by the Erica Foundation. This facility had also been started in 1934 on the initiative of the Principal, Hanna Bratt. The Foundation opened its own CGC in 1936 under the leadership of Dr Gunnar Nycander and the following year the Medical-Pedagogical Training College was opened Concurrently children with retarded development were sent for day observation and testing to the day care centre run by the YWCA, where Karin Uhlin, Ph.D., was an active member of the staff Dr Uhlin became the first psychologist to join the CGC team (1936). The addition of a child psychologist meant that the opportunities for in-depth studies of each child were greatly enlarged.

In the beginning, the focus of the work was largely directed at evaluating developmental possibilities and developing diagnostic test methods of different kinds.

Karin Selander the psychologist who joined the organization in 1944 became an extremely skillfull diagnostician during the subsequent years, especially in matters such as assessing school problems, developmental deviations and different types of intellectual handicaps. In 1948, the staff expanded to include several psychologists who were strongly orientated towards psychodynamics and therapy Elsa Jansson, who was a Rorschach specialist, and Inga Sylvander who had received her training as a child psychotherapist at the Erica Foundation. Elsa Jansson later participated as co-worker with the present author (Hans Curman) in setting up the research project which is the subject of this report. Dr

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Young people could pay regular visits to a psychologist or a doctor for more or less advanced supportive contact.

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social worker who spent 1–2 hours becoming acquainted with the parents, usually the mother and forming an impression of the nature of the case and judging its urgency Young people were sent directly to the psychologist or to the doctor

At an "intake" conference held once a week and attended by the entire team, the weekly batch of new cases was presented and therapeutic suggestions were given for each individual case. Some of the cases were given highest priority some were given relative priority and the rest were put on a waiting list which could mean a wait of six months to a year At the intake conference it was also possible to refer a particular case to some other authority e.g. a hospital, vocational guidance, the social welfare board, etc.

The subsequent case investigation—often after a shorter or longer period of waiting—was generally planned in such a way that the child [illegible] the clinic for a series (3–4) of observation [illegible]ions with the psychologist, which often in[illegible] intelligence tests and personality tests, while the parents concurrently spent time with the psychiatric social worker with whom they discussed the background and who recorded the case history As a rule, the notations were comprehensive and systematic. Even at that time, the psychiatric social worker parent relationship was regarded as a therapeutic instrument and the discussions constituted a penetration into the problems in parallel with the extraction of information. The conversations were later registered according to a stricter scheme under given headings in the patient s file.

This stage was followed by a meeting between the parents and the child and the doctor at which the child was always given a physical examination.

Each new appointment with the doctor took two hours, which meant that the doctor had plenty of opportunity of seeing the child alone—although the parents might also be present—and also of discussing the situation and the results so far obtained from the investigation with the parents. Even though the diagnosis was the predominant aspect of the investigation the attitude that diagnosis must be dealt with and exploited with a view to therapy at every step, had already been adopted.

During the working conference with the team, agreement was reached as to the measures to be taken in each single case. Some of the cases could be taken off the active list at once or after one or two further visits as "guidance cases" Supportive contact was maintained for varying lengths of time with some cases, while others received regular treatment of one type or another At that time (1953–1955), the facilities for psychotherapy consisted primarily of "play psychotherapy" measures. The procedure was such that the child spent some time—usually once a week—with a child psychotherapist, who worked with various play objects, including the World projective technique.

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As a general rule, the mother paid a visit to the psychiatric social worker or the doctor at the same time as the child was visiting with the therapist.

Our ambitions had now reached the point where we tried hard to include the father in the therapy and we managed at that time to reach about 40% of the fathers.

A certain amount of group therapy with the children was started around this time—music and painting groups, acting and rhythmics. We also applied combinations of group therapy and individual therapy Efforts were made to run group therapy even for the parents. A consultant analyst actually ran a therapy group for 13 mothers.

Mothers took part in discussion groups at which a child psychologist was present, while their children were taking part in an observation group session run by a group therapist.

subsequently in this report as the Temperance Board Register) contain information pertaining to charges of drunkenness and offences against the alcohol laws, regardless of the age of the offender

The register of Criminal Offences contains information on criminal acts which have resulted in the offender being sentenced (not minor traffic offences)

The registers kept by the child and youth psychiatric care clinics and centres and the patient registers over in-patients (subsequently referred to as the Mental Register) covers every single case that has applied for care either as an in- or an out patient at any of these institutions.

Statistical treatment

The material has been computerized. Coded data has been punched on punch-cards and later transferred to magnetic tapes and discs. The information was doubly punched and double checked against the original data to avoid errors. Programming and tabulation of the data was performed by the Systems Group of Karolinska Institutet.

In view of the fact that this work constitutes only the first stage in a long-term follow-up study for which final statistical treatment becomes possible only after a far longer period than 10 years, we have not applied sophisticated statistical methods

As the purpose has been to compare observed variables, the chi 2 test has been used in comparisons of two independent samples. The chi-2 test was also applied to relationships between different registers. For instance, if we studied the relationship between the "social" register and the "temperance" register we made the assumption that "temperance" registrations were equally common in the "social register group" as in the "non-social register group" This hypothesis was tested with the chi-2 test. If the value of chi-2 was significant, it meant that the hypothesis was not valid and that there was, in fact, a relationship between the "social" register and the "temperance" register

The following levels of significance were applied in the study

	Symbol in table	Indicating in text
$p < 0.001$		Strongly significant
$0.001 < p < 0.01$		Significant
$0.01 < p < 0.05$		Almost significant
$0.05 < p$	n.s.	Not significant

Discussion

The data presented, describing the investigation material and signifying the patients heredity familial situation home circumstances, pregnancies and deliveries, psychomotoric development early physical and mental status, and current disorders, are constructed, as accounted for in the aforegoing, partly upon the information provided by the parents or guardian at the time of the interviews. The reliability of such data can be questionable, especially with subjective and emotion fraught symptoms such as misuse of alcohol, hyperactivity anxiety lack of concentration, etc. (Dahlström 1965 Fleiss et al 1965 Kahn & Cannell 1961) In addition there are difficulties in setting up generally applicable criteria for similar data in a trial population, which means that comparisons between the frequencies for symptoms in different trial materials are always uncertain. The sources of error associated with interview methodology have, however in all probability been largely eliminated in this investigation since the interviews took place on a number of different occasions and with several different interviewers. The data registered on the statistics sheet represents the total sum of the information gathered concerning the patient and his family

Despite these sources of error clinical child psychiatry and research on clinical child psychiatry cannot do without interview methodology Apart from this, and as an aspect of considerable importance the present authors feel that a penetration of the procedures used daily in child psychiatric matters and which form the grounds upon which important decisions are based, can also provide vital information as to the future prospects for the patient.

In exploring the issues laid forth by the authors, the obvious procedure was to employ patient-register follow-up as the method of investigation. However this form of investigation technique involves not only limited possibilities for obtaining information about the individual case but also considerable methodological problems

The registers in question did not contain the wealth of detail necessary for a good assessment of the grade of difficulty and the nature of the patient s mental insufficiency and or respectively his asocial behaviour By way of example, the Register of Criminal Offences reports cases of people whose offences against the law were trite and might well have been committed on the spur of the movement never to be repeated (Elmhorn 1969) as well as cases of individuals who had committed major crimes. However it was often found that even small deviations from normal social behaviour were repeated on several occasions, which led to serious social consequences for the offender It is a well-known fact that the risk of recurrent drunkenness is large (Eklund & Nylander 1965) The present authors were faced with the problem of where to draw the line Taking into account the above viewpoints, the authors therefore decided to accept the judgments made by the institutions authorized by society Thus, when the material was analyzed, all the cases that had been reported in the Temperance Board Register were grouped together regardless of the degree of severity or the nature of the patients misuse of alcohol and the same system was applied with the other registers. This procedure might have meant that differences occurring in reality between severely criminalized individuals and non-criminalized persons, for example were eliminated entirely or at least diminished. The investigation technique would therefore have been too indiscriminate, resulting in the loss of valuable information concerning the patient. On the other hand, it can be said that when differences between criminalized and non-criminalized persons, for example, could actually be demonstrated, then there was good reason for concluding that the criminality was truly an expression of something

Attempts have in fact, been made to estimate the magnitude of this source of error Thus, data frequencies were studied and compared in the investigation covering the trial years of 1953–1954–1955 the trial subjects being divided into two groups the first group consisted of boys who had committed crimes of a more serious nature during the observation period, resulting in imprisonment for more than six months—a total of 77 cases, and the second group consisted of cases of a less serious criminal nature—a total of 99 cases Circumstances of heredity social background, environmental conditions in the home, early development and state of physical health were similar in both groups, as was the state of mental health and status except with respect to two symptoms. shoplifting and truancy occurred more often in the former group ($p <$ 0 001 and respectively $0.001 < p < 0.01$).

Another source of error might exist in the method of calculating the cumulative frequencies for mental diseases and, respectively asocial behaviour (see Chapter 6). The cumulative frequency is the total frequency of cases registered during the observation period. It can be seen from the figures on pages 36, 37 38 and 41 that a certain percentage is added annually to the different registers. Probably there are however other cases who adjust well during the year and do not require any further mental care, nor do they later behave in an asocial manner The cumulative frequency of cases, therefore, does not constitute a quantitative measure of either mental insufficiency or asociality in the trial population, but merely represents the number of people who have been in need of psychiatric help during the observation period or who have been responsible for some form of asocial behaviour that has come to the notice of the authorities. The present authors considered it to be meaningful to calculate this cumulative frequency since there is a possibility that those individuals who have never needed psychiatric care or who had not committed any form of asocial behaviour during the observation period might differ in certain respects from those who had needed psychiatric care and/or who had been registered for asocial behaviour

CHAPTER 4 DESCRIPTION OF PATIENT MATERIAL

The study included the total number of cases that had been discharged during the years 1953–1954–1955 as having completed treatment at the Child Guidance Clinic units, *in toto* 2 509 patients.

Some of these patients had, however been discharged and re-registered during the three years of the trial period In this manner 145 cases or 6 % of the total (110 boys and 35 girls) were registered more than once. The number of individuals who were actually discharged thus amounted to a total of 2 364

In accounting for the patient material for the three years in question, every single discharge has been included since the circumstances per taining to a particular case might have been different on the different occasions during these years. It was only by following this procedure that we could present a complete picture of the activities of the CGC during the three years of the trial period.

The number of discharges for the respective trial years were 741 844 and 924 thus showing annual increases of 14 % and respectively 9 %—these figures are the same for both boys and girls.

The population figures for children and young people (under the age of 20 years) within the region covered by the CGC were 194 381 for 1953 198 900 for 1954 and 204 103 for 1955 This implies that, relatively speaking, the number of children and youths discharged from the CGC was practically the same for each of the trial years, or approximately 0 4 %. In comparison, it can be mentioned that the number of discharges from the CGC in 1970 was 1 277 for a child and youth population of 166 052 individuals, corresponding to a frequency for discharged cases of 0 8 %. The difference is statistically strongly significant ($p < 0.001$).

In the following presentation of the material, the data obtained for the three years has been pooled since the analyses for each separate year showed good agreement with respect to the information required

Table 1 *Distribution according to sex and age of cases discharged from the CGC during 1953 1954 and 1955*

Sex	Age 0–6.5	6.6–11.5	11.6–15.5	15.6–	Total
Boys	343 (21 %)	721 (44 %)	419 (26 %)	151 (9 %)	1 636 (100 %)
Girls	249 (29 %)	306 (35 %)	170 (19 %)	148 (17 %)	873 (100 %)
Total	592 (24 %)	1 027 (41 %)	589 (23 %)	301 (12 %)	2 509 (100 %)

Distribution according to sex and age

The total number of cases, distributed according to sex and age are shown in Table 1

The 2 509 cases comprised 1 636 boys (65 %) and 873 girls (35 %). A study of the sex distribution for the different age groups shows that the frequency for boys was somewhat higher than that for girls at the pre-school age that it was very much higher during school age but that it was virtually the same in the highest age group

In relation to the child and youth population as a whole, the number of children contacting the CGC for aid was largest in the 6 6–11.5 years age group for both boys and girls, and smallest in the age group 15 6 years and upwards.

If a comparison is made of the sex and age distribution in the trial material from the years 1953–1954–1955 with the CGC material from 1970, it is seen that a shift in age group distribution towards higher ages has taken place and applies to both sexes. Whereas the frequency for children in the lowest age group during the years 1953–1954–1955 amounted to 24 % of the total material, this figure was only about 8 % ($p < 0.001$) in 1970 while the frequency for children in the oldest of the age groups in 1953–1954–1955 was about 12 %, it reached 39 % in 1970 ($p < 0.001$). The largest increase was found for girls in the highest age group, rising from about 17 % to about 49 % ($p < 0.001$).

Distribution according to social class

The distribution of the trial material according to social class, using the same grounds for social class adherency as were used in the Stockholm municipal elections in 1954 does not deviate from the social class distribution valid for married male voters. The distribution for the boys was similar to that for the girls.

The cases falling under the authorization of the CGC and treated at the office of the Social Welfare Medical Officer and at the guidance clinics attached to the children's homes, have not been included in the trial material. These cases, who were mostly children and young people coming from socially inadequate environments classed as social class 3 and children and young people with very considerable problems of adjustment, could not be investigated and examined as completely and systematically as was required to be eligible to be included in a follow-up study of the model used here

Domestic circumstances

In 1 939 cases (77 %), the child was living at home with both its father and its mother while 508 cases (20 %) lived at home with only the mother 32 cases (approx. 1 %) lived with only the father and 7 cases resided at children's homes. This distribution was more or less applicable for both boys and girls, and for the various age groups. Even in the lowest age group the children—both boys and girls—were noted as living at home with only the father for example.

Every tenth child (238 or about 10 %) was a stepchild while a few were adopted (50 or about 2 %) or taken as foster children (52 or about 2 %). The frequency for stepchildren was equally distributed between the three social classes, about 3/4th of the adopted children were living in the upper and middle class environments, and more than half the number of foster children were living in lower class homes.

Approximately 12 % or 299 cases were illegitimate the frequency for illegitimate children was lowest in social class 1 with about 5 %, followed by about 9 % in social class 2 and, subsequently the highest frequency of about 16 % for social class 3

In 520 cases, or approximately 21 %, the child—boys just as often as girls—had experienced a divorce situation. Whereas the number of girls coming from broken homes was largely the same in all three social classes, the number of boys coming from broken homes was almost twice as great in social group 3 as those from social group 1 (25 and, respectively 13 %) ($p < 0.001$).

The death of a parent had occurred in a total of 146 cases in 110 cases or about 4 % of the total material, it was the father who had died and in 36 cases, or about 2 %, it was the mother The incidence was the same for boys and for girls, and for the different age groups.

The number of working mothers represented about 1/4th or approx. 27 % of the total number of mothers, and were found more often in social classes 2 and 3 than in social class 1 the percentages being 31 % and 27 %, and, respectively 19 %, and being similar for both boys and girls.

Mental disease had been reported to the same extent for fathers as for mothers (4 %), but records of neurotic disturbances were more frequent for mothers than for fathers (approx. 16 % against 8 %, $p < 0.001$) On the other hand, the fathers were noted as being misusers of alcohol or narcotics more frequently than the mothers (7 %) and also for a higher percentage of asocial behaviour (approx. 3 %), the registration figures for alcoholism and asocial behaviour for the mothers being only 18 cases or about 1 %. A few of the parents were retarded (11 fathers and 27 mothers, or 0.4 and 1 % respectively) Mental disease occurred with equal frequency in the different social classes, as did neurotic disturbances, while inhibited development and misuse/asociality were reported more often in social class 3 than in social class 1

The incidences for mental diseases and insufficiencies, inhibited development and misuse/asociality in the parents did not show any significant differences when related to boys or girls or the different age groups.

"Disharmonious marriages" were stated in

about 14 % of all the cases, and was equally common for girls as for boys and occurred just as often for the children in the lower age groups as for those in the upper age groups.

Perusal of the corresponding values for the 1970 trial material reveals that there is good agreement between the two studies.

Discussion

The patient material applying for aid at the CGC during the trial years of 1953–1954–1955 was not representative of those persons who during the same period, applied for aid at the out patient child psychiatric units in Stockholm. At this time, child psychiatric care was available not only at the CGC centres but also at the office of the Social Welfare Medical Officer attached to the Child Welfare Committee at the guidance sections of the children's homes, at the Kronprinsessan Lovisa's Children's Hospital (KLB) and at the Erica Foundation. The CGC took on about 60 % of the cases who during the period in question, were subjected to child psychiatric examination and/or treatment. The majority of the children and young people who came from gravely disturbed environments and/or who were suffering from severe social maladjustment problems were referred to the Social Welfare Medical Officer and to the guidance sections of the children's homes. The cases that were examined at KLB comprised to a large extent patients referred to child psychiatric care as outpatients by medical and surgical children's departments at the hospital, on the grounds of psychosomatic symptoms or delayed development (Nylander 1959). At the time of the study in question, the Erica Foundation took fees for examination of patients and subsequent treatment, so that the clientele was clearly dominated by persons from the upper and middle social classes (Nycander 1950). In summarizing, it can therefore be said that the CGC clientele did not include those individuals in the worst social position, those with the least advantages, or those who were socially maladjusted, and that children with fixed and severe psychosomatic symptoms as well as children who were retarded were most probably underrepresented.

With a few exceptions, the data presented in the aforegoing has been taken from official registers, the Population Census Register hospital registers, etc., and can therefore be assumed to provide highly reliable information. The values given correspond largely to those obtained for Swedish child psychiatric clientele in out patient care (Curman et al. 1958) and do not deviate to any significant degree from the comparable figures for the mean population according to the official statistics. As in all child psychiatric patient materials, the boys predominate. This applies particularly to the school age group in which the boys represent 71 % and the girls 29 % of the total (for the pre-school age group the corresponding frequencies were 58 and 42 %, and for the post-school age group these were 51 and 49 %, respectively).

CHAPTER 5 PRESENTATION OF DATA FROM THE YEARS STUDIED 1953–1954–1955

Route of contact patient–CGC

The staff of the CGC were of the opinion that it was important for those persons applying for help (parents) to have a motive of their own for taking this step and that the applicants themselves should make the contact with the CGC. This attitude is generally accepted by the Child Welfare Committee, by the schools and by the paediatricians practising in the city of Stockholm. A presentation of the persons registered as having requested an examination merely illustrates the formal pathway to making contact with the CGC. Many of the cases registered as having made contact with the CGC on their own

Table 2. *Symptoms registered for the patient material*
Figures within parentheses denote percentages

	M	F	M–F
Delayed development	168 (10.3)	83 (9.5)	251 (10)
Epileptic-type fits	41 (2.5)	25 (2.9)	66 (2.6)
Spasticity, paresis, other neurological symptoms	21 (1.3)	6 (0.7)	27 (1.1)
Headaches	116 (7.1)	62 (7.1)	178 (7.1)
Cardiac symptoms	17 (1)	12 (1.4)	29 (1.2)
Respiratory distress	43 (2.6)	27 (3.1)	70 (2.8)
Navel colic	176 (10.8)	115 (13.2)	291 (11.6)
Encopresis	107 (6.5)	32 (3.7)	139 (5.5)
Enuresis	376 (23)	148 (17)	524 (20.9)
Tics, compulsory movements	190 (11.6)	59 (6.8)	249 (9.9)
Compulsive actions	54 (3.3)	34 (3.9)	88 (3.5)
Depressions, apathy, inhibitions	100 (6.1)	80 (9.2)	180 (7.2)
Refusal to eat	244 (14.9)	151 (17.3)	395 (15.7)
Night terrors, fear	197 (11.7)	105 (12)	297 (11.8)
Insomnia	308 (18.8)	207 (23.7)	515 (20.5)
Speech defects, mutism	219 (13.4)	70 (8)	289 (11.5)
Habitual manipulations	478 (29.2)	294 (33.7)	772 (30.8)
Excessive masturbation	36 (2.2)	23 (2.6)	59 (2.4)
Relationship difficulties	491 (30)	279 (32)	770 (30.7)
Mother fixation, anxiety	562 (34.4)	341 (39.1)	903 (36)
Hyperactivity	435 (26.6)	141 (16.2)	576 (23)
School fatigue, unwillingness to work	176 (10.8)	94 (10.8)	270 (10.8)
Confabulation	98 (6)	59 (6.8)	157 (6.3)
Obstinacy, negativism	493 (30.1)	300 (34.4)	793 (31.6)
Aggression towards siblings and parents	307 (18.8)	176 (20.2)	483 (19.3)
Aggression towards older people and peers	214 (13.1)	55 (6.3)	269 (10.7)
Temper tantrums	109 (6.7)	69 (7.9)	178 (7.1)
Attempted suicides	15 (0.9)	19 (2.2)	34 (1.4)
Destructive behaviour	69 (4.2)	16 (1.8)	85 (3.4)
Vagabondage, running away from home	68 (4.2)	28 (3.2)	96 (3.8)
Truancy	154 (9.4)	38 (4.2)	191 (7.6)
School phobia	9 (0.6)	8 (0.9)	17 (0.7)
Disruptive at school	214 (13.1)	29 (3.3)	243 (9.7)
Incapable of following tuition	227 (13.9)	78 (8.9)	305 (12.2)
School immaturity	476 (26.0)	121 (13.9)	547 (21.8)
Difficulties in learning to read and write	255 (15.6)	75 (8.6)	330 (13.2)
Shoplifting, theft	251 (15.3)	79 (9)	330 (13.2)
Stealing cars and motorbikes	16 (1)	— (—)	16 (—)
Arson	29 (1.8)	1 (—)	30 (—)

initiative (relatives, the patient himself/herself) had very likely applied as a result of encouragement by others.

Of the 2 509 cases, 2 076 (83 %) had applied through relatives while 39 (2 %) had personally got in touch with the CGC. The number of cases referred to the CGC by the schools was 157 (6), 88 cases (4 %) by the Child Welfare Committee, 59 cases (2 %) by some other social welfare authority, 75 cases (3 %) by hospital doctors, and 15 cases (1) by some other source. There were no differences with respect to the sex of the patient in the way in which contact was made.

Symptoms registered

The symptoms registered as prevailing at the time of the examination are given in Table 2. In a very few cases, only one symptom was recorded, but the majority of the cases had several symptoms—the average number for the entire material was about 4 symptoms per individual.

Common symptoms which led to contact with the CGC were delayed development, abdominal

pains of the navel colic type, enuresis, tics, refusal to eat, insomnia, speech defects, habitual manipulations, difficulties in making and maintaining contacts, mother fixation, hyperactivity, aggressiveness, inability to follow tuition, difficulties in learning to read and write and shoplifting and/or theft, the frequencies for all these symptoms being in excess of 10% of the whole material.

The majority of these symptoms were registered just as often for boys as for girls: delayed development, navel colic, refusal to eat, habitual manipulations, relationship problems, mother fixation, school fatigue, obstinacy and negativism, and aggressiveness. Some of the symptoms occurred with significantly greater frequency among the boys as compared with the girls: enuresis ($p < 0.001$), encopresis ($0.001 < p < 0.01$), tics, speech defects, hyperactivity, truancy, disruptive behaviour at school, inability to follow tuition, difficulties in learning to read and write and shoplifting and theft ($p < 0.001$ for all the aforegoing symptoms). Other symptoms—depression ($0.001 < p < 0.01$) and insomnia ($0.001 < p < 0.01$), were however registered more often among the girls.

Certain symptoms showed a clear tendency to diminish with increasing age, both for boys and for girls: delay in development, enuresis, encopresis, refusal to eat, speech defects, habitual manipulations and hyperactivity. Other symptoms occurred more frequently among the older children, both boys and girls: depression, confabulation, attempted suicide, inability to follow tuition, reading and writing problems, truancy, vagabondage, running away from home and shoplifting. In the case of other registered symptoms, there were no certain significant differences in the frequencies for the different age groups.

If a comparison is made with the symptoms registered for the trial material and those obtained from the CGC study from 1970, it can be seen that certain symptoms occurring more frequently in the younger children than in the older ones were registered altogether less frequently in 1970 as compared to the 1953–1954–1955 study (delayed development, encopresis, enuresis, refusal to eat, speech defects, habitual manipulations, obstinacy and negativism—$p < 0.001$) whereas other symptoms which occur more often in the higher age groups than in the lower age groups are registered more often in 1970 than in the 1953–1954–1955 study (depression—$p < 0.001$ and attempted suicide—$0.001 < p < 0.01$).

Psychological examination and investigations

In order to clarify the status of the patients, 2 130 cases were given development tests and/or intelligence tests—these represented about 85% of the total material.

The Terman-Merrill (TM) test was given to about 62%—1 556 children = 1 091 boys and 465 girls. The results indicated an IQ distribution with an overrepresentation of individuals with IQ 110 and above, roughly the same for both boys and girls (cf. Jonsson & Kälvesten 1964). By way of comparison, it can be mentioned that only 216 (about 17%) out of the 1 277 cases that were discharged in 1970 had been studied by means of the Terman Merrill test.

In 77 cases (56 boys and 21 girls), the TM tests were supplemented with different non-verbal, performance tests. The results of these tests showed good agreement with the results of the TM-tests.

A limited number of cases (161 cases) were studied by means of the Bühler–Hetzer tests—the subjects were mostly very young children. The results indicated that the distribution for the development quotients was within the normal range, and was the same for both boys and girls.

Other methods were applied to a few other cases in order to obtain an estimation of levels of intelligence and development.

In 25 cases (17 boys and 8 girls) the child's development was so disturbed that it was not possible to complete a proper testing.

As difficulties in learning to read and write were suspected in 270 children (211 boys and 59 girls), corresponding to 11%, the writing and reading tests devised by the CGC were given to these children.

Personality assessments included a non-structural play or conversation situation and a number of projective test methods such as the World projective technique, CAT TAT Machover etc. A total of 985 cases (659 boys and 326 girls) were studied by this means, representing about 39 % of the material. Of these children, 82 boys and 28 girls were more than 11.5 years of age

Rorschach tests were used in a total of 747 cases (520 boys and 227 girls), corresponding to about 30 % of the total. With the exception of the very youngest age group in which only 18 cases were studied, this method was employed to the same extent in all the age groups.

Treatment and measures taken

Contact with the patient and his/her closest relatives in connection with the case investigation and the subsequent summarization, also involved some form of treatment the applicants had the opportunity of discussing their problems, of making personal contacts and receiving support and advice and new impulses which enabled them to strive towards a solution of the conflict situation.

In some cases, the problems were such that simple discussions on one, or a few occasion(s) were sufficient to help the applicant. For example, the consultation might have dealt with problems concerned with reading and writing, resulting in proposals for pedagogical measures the consultant may have been required to act as mediator in referring the applicant to some other institution e g. for vocational guidance family counselling or a child psychiatric clinic. Upon occasion, the patient himself has broken off relations with the CGC after a single visit, or only a few visits, the reason in most cases being unknown.

In the vast majority of cases, the contact has involved both the patient and the patient s mother In a few cases, all teenagers, the patient has however come on his own initiative and has specifically declined the involvement of other parties. In 921 cases, or approximately 37 % of the total material, contact was also made with the patient s father (the frequency was more or less the same for both boys and girls, and for the patients in the different age groups). It should, however be remembered that single mothers comprised 20 % of the applicants.

Continuous supportive contact with the parents and their children was maintained in 1 064 cases (746 boys and 318 girls), representing 42 of the total material In some cases this contact has been maintained for a number of years.

Play therapy was employed in 139 cases (85 boys and 54 girls), or about 6 of the total material. In this group, 69 of the boys and 40 of the girls belonged to the younger age groups (up to 11.5 years). On an average, play therapy was pursued for 1–2 years (range 6 months to 6 years), with a tendency towards shorter therapy periods for the younger children, as compared with the older children in this category and for the same length of time for both boys and girls.

In 181 cases (128 boys and 53 girls), or approximately 7 % of the total material, the patients attended group therapy—most of these children belonged to the three younger age groups (98 %). In these cases also the therapy period continued for 1–2 years (range 6 months to 7 years). Even some of the parents—a total of 70 cases, relating to 45 of the boys and 25 of the girls, about 3 %— attended group therapy or "circles"

In 383 cases (265 boys and 118 girls—approx. 15 %), the CGC made contact with the patient s school and proposed measures such as delaying school attendance special remedial classes, changes of class or school and so forth.

In 295 cases (201 boys and 94 girls—approx. 12 %), the CGC made contact with the Child Welfare Committee offering recommendations relating to supportive social measures, surveillance or reform school care

Diagnoses

Following the investigation, each patient was given a primary diagnosis (only one diagnosis for each case), i.e. the nature of the patient s symptoms or the state of insufficiency existing were registered.

The symptoms were classified according to seven groups *healthy children* (children with un-

Table 4 *The distribution of the trial material according to sex and age at the time of the conclusion of the follow up study*

Age	10–16.5	16.6–21.5	21.6–25.5	25.6–	Total
Boys	304	656	384	133	1 477
of total number of boys	20.6	44.4	26	9	100
Girls	222	289	150	130	791
of total number of girls	28.1	36.5	19	16.4	100
Total	526	945	534	263	2 268
	23.2	41.7	23.5	11.6	100

In 50 of these cases (23 boys and 27 girls) the case-history had not been followed through with detailed notations. Twenty-six cases (10 boys and 16 girls) had left the country during the observation period

In 20 cases (16 boys and 4 girls) the patient had died during the observation period (0 8 %) The causes of death were somatic disease in 8 tumor cerebri in 2 cases, 1 case of hydrocephalus, 1 case of cerebral abscess, 1 case of lymphogranulomatosis maligna, 1 case of malignant neoplasm in the lungs with metastases, 1 case of congenital VOC, and 1 case of fatal bleeding in connection with a total ventricle resection in a diabetic boy suffering from ulcus In 7 cases (all boys) the cause of death was reported to be accidental, the accident itself resulting in head injuries or drowning. In 5 cases (3 boys and 2 girls) the cause of death was suicide

The distribution of age and sex in the patient *material that was followed up during the course* of the 10 years following the discharge of the patient from the CGC, is shown in Table 4 It can be seen from the table that a total of 2 268 cases (1 477 boys or 65 %, and 791 girls or 35 %) could be followed up The distribution according to age and sex is more or less the same as in the trial material.

Noted in the Register of the Temperance Board

A total of 209 cases (192 boys and 17 girls) or 9.2 % of the material as a whole (13 % boys and 2.1 girls) had been noted in the Register of the Temperance Board by the end of the observation period because of one or more drunkenness offences.

Table 5 shows the year after discharge when the offender was registered in relation to his age at discharge from the CGC. The data in this table refers to the boys in this category It can be seen from the table that the youngest boy was 12 years old when he was registered, registration taking place 2 years after his discharge from the CGC. The average age for registration was approximately 18 years (range 12–26 years). The table also shows that the risk of registration was relatively small for the boys who were under the age of 10 years at the time of their discharge, but that from the age of 10 years onwards, the incidence of registered cases were about 20 % but that it does not rise much above this level afterwards.

Table 6 accounts for every case that was registered for drunkenness offences on one or more occasions. The youngest of the sparse *number of girls registered was 13 years old and* the average age at the time of registration was around 20 years (range 13–28 years)

It can be seen from the table that about 45 % of the boys who had been registered were guilty of drunkenness on only one occasion, about 31 % of them on 2–3 occasions, about 21 % on 4–10 occasions and about 4 % committed drunkenness offences on more than 10 occasions.

Among the registered girls, one was charged with recurrent drunkenness on 2–3 occasions and four of them on 4–10 occasions.

The risk of recurrence among the boys (the risk of being registered for a second or third offence is obtained if the number of cases charged

Table 5 *Year of registration in the Register of the Temperance Board for boys in relation to age at discharge*

Years after discharge	Age at discharge (years) 3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
1													1					
2								1				3	4		2		1	
3									1	2	1	1	2			1		1
4								1	3	3	2	5	2	3		1		
5								2	4	5	5	2	1	1				
6							1	3	8	4	3	2	2	2	1			1
7					1	3	2	4	3	9	4	2					1	
8						8	4	6	4	3	1		2					
9			1		2	2	5	2	5	3	1	2						
10		1		2		3	3	8	3	1	1		1	1				
of total number in age group		1	1	2	2	14	12	21	23	25	18	25	22	16	—	—	—	—

Table 6. *Drunkenness offences registered during the observation period*

No. of reports to temperance board	Age at discharge from the CGC (years) 0–6.5 M 304	F 222	6.6–11.5 M 656	F 289	11.6–15.5 M 384	F 150	15.6– M 133	F 130	Total M 1 477	Total F 791	Total M+F 2 268
1 report	2	—	42	6	34	2	8	4	86	12	98
2 3 reports	—	—	23	—	27	—	9	1	59	1	60
4–10 reports	1	—	14	—	21	1	4	3	40	4	44
More than 10 reports	—	—	—	—	7	—	—	—	7	—	7
Total no. of reports	3	—	79	6	89	3	21	8	192	17	209
I of total no. in age group	1	—	12	2	23	2	15	6	13	2	9

for a second or third offence is placed in relation to the number having committed only one offence) was 69 %, while the risk for 4 to 10-time offenders was 68 % and for more-than-10-time offenders the figure was 18 %. No risk calculations were made for the girls as they were so few

Figure 1 illustrates the cumulative percentage of boys who were registered during the observation period. It can be seen that only one boy was registered during the year immediately following the year of discharge but that the percentage of registrations for the boys increases continuously after this time, the annual increase being between 1–2 % of the total number of boys and reaching the figure of 13 % of the total in the 10th year after discharge.

Three cases of grave alcoholism are reported as case-histories in the supplement (page 57).

Notations in the Social Welfare Board Register

At the conclusion of the observation period, 639 persons out of the total number of 2 268 patients had been registered in the Social Welfare Board Register this figure corresponding to 28.2 % of the total (499 boys or 33.8 %, and 140 girls or 17 7 %).

Table 7 gives the reasons for contact being made with the social welfare authorities.

It will be observed from the above table that the boys come into contact with the social welfare authorities chiefly because of criminal acts, while other reasons are valid for the girls (need of supportive measures, etc.).

The frequency for criminal offences among the boys is relatively low in the lowest age group, 0–6.5 years (approx. 10 %), and highest in the

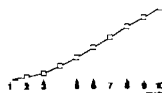


Fig 1 Cumulative percentage of boys noted in the Temperance Board Register during the observation period (in years).

11 6–15.5 years group with about 30% of the total number of boys being registered In the case of the girls, the figures for criminality were w for all the age groups. The frequency of boys ho were in need of supportive measures supplied by the social welfare authorities was highest n the lowest age group with about 19% of the total number of boys being registered but subsequently fell continuously with increasing age The frequency for the girls showed the opposite trend with the lowest frequency in the lowest age group, followed by a continual rise through the higher age groups.

Table 8 shows the point of time during the observation period when the boys were registered owing to criminality· the registrations in the social register are given in relation to the number of years following discharge and the age of the patient upon discharge. The mean age of the material at the time of registration was approximately 14 years (range 8–20 years) The few girls who were registered for criminality showed a similar distribution, with a mean age upon registration of approximately 16 years (range 13–20 years) In calculating the frequency of registrations for criminality in the social register for the boys according to the age distribution upon discharge it is seen that the frequency is low for the boys who were discharged at the age of 2 years and that this figure proceeds to rise until it reaches a peak among those boys who were discharged at the age of 10–12 years.

Figure 2 presents the cumulative percentage of boys registered in the Social Welfare Register owing to criminality It can be seen that the frequency of cases who were registered 1 year after discharge corresponds to 5% of the total number and that this figure increases continuously by about 1–2% per annum until it reaches the maximum percentage of 21% in the 10th year after discharge.

Supplement (page 56) gives an account of the measures taken as a result of the reports of child criminality

Three cases of grave social maladjustment are reported as case-histories in Supplement 3 (page 58).

Notations in the Criminal Offences Register

During the observation period, a total of 187 patients—(176 boys and 11 girls) or approximately 8% of the total material—where reg

Table 7 *Causes for contacting the social welfare authorities*

	Age at discharge (years)							
	0–6.5		6.6–11.5		11.6–15 5		15.6–	
	M	F	M	F	M	F	M	F
Child criminality	31	5	150	17	116	10	16	4
.. of total in age group	10	2	23	6	30	7	12	3
Other causes	57	25	89	37	31	22	9	20
of total in age group	19	11	14	13	8	15	7	15

Table 8. *Year of registration in the Social Welfare Board Register (criminality) for boys, in relation to age at discharge*

Years after discharge	Age at discharge (years) 2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
1						1	1	2	6	10	12	17	10	10	6	4	1	1
2						1	1	3	6	13	7	3	2	2			1	
3				1		2	2	4	6	3	10	3	3	1		1		
4					1	2	1	4	8	4	3	3						
5			1	1	2	1	3	3	7	6	6	1						
6			2		3	4	2	1	2	6	2							
7			1	2	3	3	5	6	2		1	1						
8			1		2	4	10	4	1	1	2							
9	1	1	1	5	3	3		1	2									
10		1	1	4	2	3	1											
% of total number i age group	3	6	10	13	15	15	23	23	31	32	36	28	22	19	14	17		

istered in the Criminal Offences register the figures corresponding to 11 9 % for the boys and 1 4 % for the girls. If the frequency is calculated for those who reached legal age when they were personally responsible for their acts and thus eligible for penal measures (15 years) during the observation period, the percentage for the entire material is 8.9 %, 13.2 % for the boys and 1.5 % for the girls.

Supplement 2 (page 57) gives an account of the type of criminal acts that led to registration. Crimes of theft were the dominating category and corresponded to about 75 % of the total. The notations in the register were classified according to the "principal offence"

None of the children who were discharged be tween the ages of 0–6.5 years are to be found among those registered (the majority of these cases had not reached legal age during the obser vation period). Among the boys in the age group 6.6–11 5 years, 10 1 % had been registered, 21 4 % in the age group 11 6–15.5 years, and 21 1 % in the age group 15 6 and upwards. The corre- sponding frequencies for the girls are 0 7 %, 2.7 and 3 8 %.

Table 9 shows which year during the observa- tion period that the boys were registered, with the material grouped according to age at the time of discharge The mean age of the boys at the time they were registered was approximately 19 years (range 15–28 years), and approximately 21 years for the girls (range 15–24 years). It can also be seen from this table that the frequency of registered cases reaches its peak for the boys who were as young as 10 years at the time of their discharge from the CGC.

The cumulative frequency for boys registered in the Register of Criminal Offences during the observation period is illustrated in Figure 3 For the sake of comparison the percentage has been calculated on the total material regardless of

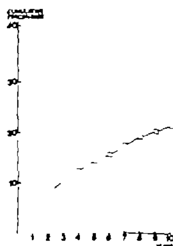


Fig 2. Cumulative percentage of boys noted in the Social Welfare Register owing to criminal activities during the observation period (10 years).

Table 9 *Year of registration for boys in the Register of Criminal Offences, in relation to age at discharge*

Years after discharge	Age at discharge (years) 7	8	9	10	11	12	13	14	15	16	17	18	19
1									1		1	1	1
2									1	3		1	1
3						1	2	1	2	2			
4						2	3	3	4	1			
5					2	3	6	5	2	1	1	1	
6				2	4	9	2	3		1	2		1
7		2	1	5	12	3	4	3	1				
8		4	5	10	2	3	2		1				
9	2	4	5	5	4	2	1		1				1
10		1	4	4	3	1	1			2		1	
% of total number in age group	1	10	12	20	20	20	21	22	19	23	—	—	—

whether all the patients had reached legal age during the observation period. It can be seen from the figure that the cumulative percentage of boys registered in this Register rises continuously after the first few years of the observation period, increasing annually by 1–2 % and reaching the peak figure of 11 9 % in the 10th year after discharge.

Total registrations of criminal offences by boys

Some of the boys who were registered in the Social Welfare Board Register for criminality during the observation period were also registered concurrently in the Register of Criminal Offences, but other boys were not burdened by such double registrations. A compilation of those cases with notations in the social register only (for criminality) with those cases who had been registered in the criminal offences register gives the total number of boys to be registered for criminality during the observation period. The figure thus obtained totalled 372 cases or approximately 25 % of the entire material In the age group that was up to 6 5 years at the time of discharge, the frequency was about 10 %, the frequencies for the other age groups were approximately 26 % for the 6 6–11 5 group, approximately 36 % for the 11 6–15.5 group and about 26 % for the oldest group of 15 6 years and upwards.

Three cases of grave criminality are presented as case-histories in Supplement 3 (page 59).



Fig 3 Cumulative percentage of boys noted in the Register of Criminal Offences during the observation period (in years).

Information from the Recruitment and Replacement Office of the Swedish Armed Forces

Information obtained from the Recruitment Register revealed that 1 003 boys out of the total of 1 477 had been recruited for their compulsory military service during the observation period During this time, 844 boys or about 84 % completed part or all of their stretch of duty Of the remaining 159 cases, 128 boys or about 13 % of the total were freed from military

Table 10. *Number of cases applying for psychiatric care during the observation period (absolute figures and percentage of the total number in the age group)*

	Boys					Girls				
Age at discharge (years)	0–6.5 304	6.6–11.5 656	11 6–15.5 384	15 6– 133	Total	0–6.5 222	6.6–11.5 289	11 6–15.5 150	15.6– 130	Total
Applied for psychiatric care, total	102	230	103	29	464	52	97	50	56	255
	33.6	35 1	26.8	21.8	31 4	23 4 %	33.6	33.3	43.1	32.2
Outpatients	82	197	90	23	392	46	83	49	44	222
	27 %	30	23 4	17 3	26.5 %	20 7 %	28.7	32.7	33.8	28.1
Inpatients	30	49	36	13	128	5	12	15	26	58
	9.9	7.5	9 4	9.8	8.7	2.3	4.[illegible]	10	20	7.3
Child psychiatric outpatients	82	190	72	10	354	45	75	30	15	165
	27	29	18.8	7.5	24	20.3	26	20	11.5 %	20.9
Adult psychiatric outpatients	1	14	32	14	61	2	19	28	37	86
	0.3	2.1	8.3	10 5	4 1	0.9	6.6	18.7	28.5	10.9
Child psychiatric inpatients	29	38	14	—	81	5	10	4	1	20
	9.5	5.8	3.6	—	5.5	2.3	3.5 %	2.7	0.8	2.5
Adult psychiatric inpatients	1	16	25	13	55	—	4	14	25	43
	0.3	2.3	6.5	9.8	3.7	—	1 4	9 4	19.2	5.4

service on the groups of "mental handicap" and 31 boys or about 3 % of the total were freed on the grounds of "physical handicap"

The remaining 474 were too young to be eligible for military service or (a few) were not eligible as they were not Swedish nationals.

Applications for psychiatric care

During the observation period a total of 719 cases or about 32 % of the entire material had applied for psychiatric care, the figures being similar for boys and girls (31 4 and 32.2 %, respectively) (see Table 10)

While the frequency of relapses among the boys fell from 33 6 % for the group that was between 0–6.5 years at the time of their discharge from the CGC to 21 8 % ($p < 0.001$) for the group that was upwards of 15 6 years, the trend was the reverse for the girls (from 23 4 to 43 1 %, $p < 0.001$). Similarly the frequency of cases requiring hospitalization was largely the same for both boys and girls (8 7 % and 7.3 %, respectively), but whereas the frequency was at more or less the same level for all the age groups with respect to the boys, it was at a low level (2.3 %) for the youngest group of girls and proceeded to rise continuously up to the oldest group (20 %), ($p < 0.001$).

It was also found that while the majority of the boys who had applied for psychiatric hospital care had previously required hospitalization at a child psychiatric clinic, the girls had received treatment more frequently as in-patients at psychiatric clinics. (N B. a number of cases had applied for both child psychiatric care and psychiatric care during the observation period).

The frequency of cases who were registered with the Care Organization for Feebleminded during the observation period was low for both boys and girls (1 7 % and 1 1 %, respectively).

The frequency of cases who were granted pensions owing to physical handicaps during the observation period was also low for both sexes (1 1 % for the boys and 1 9 % for the girls).

Table 11*a* and *b* shows the time when the first contact was made between the patients and the psychiatric care organization. The *a* table gives the data for the boys and the *b* table the data for the girls. The material is presented in relation to the age of the patient at the time of his/her discharge from the CGC. It can be seen from the table that the larger part of the material, somewhat more than half the clientele, applied for care during the first two years after their discharge from the CGC, the actual figures being very similar for both boys and girls. In subsequent years, the number of applicants increases annually by about 2 % of the total population,

Table 11*a*. *Time of registration in the Mental Register for boys the material presented in relation to age at the time of discharge*

Observation period (years)	Age at discharge (years) 0–3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
1	8	9	5	16	21	11	17	15	11	9	10	10	5	2	4	2	4
2	5	7	8	7	7	8	5	11	8	9	4	2	2	—	1	2	—
3	4	3	6	4	6	3	6	4	3	2	1	3	—	2	—	—	—
4	1	2	4	2	8	5	2	3	4	2	3	2	—	—	—	—	—
5	1	1	1	2	3	—	3	6	2	2	1	—	—	1	—	—	—
6	—		1	3	2	4	2	1	1	2	2	2	—	—	—	—	—
7	—	1	4	1	3	3	1	2	2	—	—	—	—	—	1	1	1
8	—		3	2	2	4	3	3	3	2	—	—	2	—	—	—	1
9	2	2	3	3	3	3	[illegible]	1	—	1	2	1	—	2	2	—	—
10	1	1	—	3	—	—	2	3	1	3	2	1	1	—	—	—	1
No time given										1		1					
of total number in age group	31	37	33	40	33	36	36	38	25	28	25	32	15	16	35	39	26

Table 11*b* *Time of registration in the Mental Register for girls, the material presented in relation to age at the time of discharge*

bservation riod (years)	Age at discharge (years) 0–3	4	5	6	7	8	9	10	11	12	13–15	16–18	19–
1	3	6	3	6	10	2	4	3	5	3	23	16	6
2	3	3	1	2	3	3	1	5	3	1	6	3	2
3	3	1	1	—	1	3	1	1	3	1	2	1	—
4	—	1	1	—	1	2	—	—	2	—	3	3	2
5	2	—	2	1	2	—	1	1	2	—	2	1	1
6	1	—	—	2	1	2	3	1	—	—	7	4	1
7	2	2	—	—	3	1	2	3	2	—	1	—	4
8	—	—	—	1	2	3	2	—	—	—	4	—	1
9	2	2	—	1	2	1	1	1	—	—	1	—	—
10	1	2	2	—	3	2	—	—	—	—	2	—	—
No time given				1									
of total number in age group	23	35	16	20	33	37	33	35	37	16	40	36	59

in this case too, the figures being similar for boys and girls. (See Figure 4.) The table shows that the relationship between relapses during the observation period and the age of the patient upon discharge is weak.

Supplement 6 (page 71) reports the diagnoses found during the examinations of the patients performed during the observation period. The total number of diagnoses does not correspond to the number of actual cases who applied for psychiatric care since some patients were diagnosed more than once. It can be seen from the table that the diagnostic panorama is more or less the same for the boys as for the girls. The commonest notations were "behaviour disorder environmental reactions" representing the diagnosis for about 16% of all the boys and about 15% of all the girls. This is followed by "neurosis" for about 10% of the boys and about 12% of the girls. "Developmental deficiencies" were found for about 4% of the boys and about 5% of the girls, and "character disorders" for about 4% of the boys and about 2% of the girls.

It is of particular interest to note that, during the follow-up period, a diagnosis of "psychosis" was found for about 1% of the boys (15 cases)

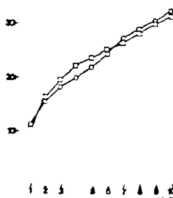


Fig 4 Cumulative percentage of cases noted in the Mental Register during the observation period (in years) (boys = □ girls = ○).

and about 2% of the girls (15 cases). During the follow-up period, 6 of these 30 cases received their diagnosis at a child psychiatric clinic but later on not in adult psychiatry. Twenty cases were registered only in the adult psychiatric register during the same period. Finally the remaining 4 cases were considered to be "psychotic" by both the child psychiatrist and, later by the adult psychiatrist during the follow-up period.

Among the cases of psychosis 7 cases (5 boys and 2 girls) displayed a picture of "child psychoses" They all showed the same symptoms from infancy or from the young child stage delayed development, particularly with respect to speech, hyperactivity different forms of stereotypy outbursts of temper personal contact difficulties and withdrawal. All of these cases required institutionalization for shorter or longer periods.

Twelve cases (6 boys and 6 girls) developed schizophrenia for which they were hospitalized and treated at either a psychiatric clinic or a mental hospital. The symptomatic picture of schizophrenia became manifest earliest in a boy who was 14 years old (the average age of the debut was about 17 years for the boys (range 14–19 years) and about 19 years for the girls (range 16–21 years)). In all the cases, the manifestation of the disease was preceded by uncharacteristic symptoms for which help had been requested at the CGC whining and crying, enuresis, hyperactivity poor personal relationships, aggressiveness and disruptive behaviour at school, insomnia, masturbation and hyper sensitivity Three of these cases received a diagnosis of psychoses at the time of their discharge from the CGC.

Some of the patients who applied to the CGC during the years 1953–1954–1955 developed affective psychoses (3 boys and 3 girls) They were all hospitalized and treated at either a psychiatric clinic or a mental hospital. The diagnosis for three of these patients (1 boy and 2 girls) was psychosis manica or respectively mania, while the remaining three were diagnosed as manodepressive psychosis. Two of the latter patients exhibited depressive symptomatology (1 boy and 1 girl) and the third patient's illness ran a biphasic course These cases had also exhibited non-specific nervous symptoms before succumbing to their psychoses, in most cases the symptoms were apparent from very early in their lives in the form of hyperactivity "willfulness" whining and crying, refusal to eat, aggressiveness, shoplifting, "tiredness" attacks of anxiety "sloppiness" etc. Three of these cases were diagnosed as psychotics upon their discharge from the CGC.

An uncharacteristic symptomatic picture was reported in 5 cases (1 boy and 4 girls). One of these patients was a mentally retarded girl who, after her discharge from the CGC, was hospitalized at a psychiatric clinic with the diagnosis of psychosis puerperium one of the other patients, a girl with retarded development, was studied at a psychiatric clinic after her discharge from the CGC and diagnosed as psychotic as a result of a brain tumour another girl with a neurotic disposition was considered to be hysterical and was admitted to a child psychiatric clinic two years after she had been discharged from the CGC, and subsequently diagnosed as psychotic due to epilepsy a third girl, a talented emigrant child who had applied for help in 1954 because of difficulties in learning to read and

Table 12. *Relationship between the different registers with reference to boys between the ages of 6.6–11.5 years at the time of their discharge from the CGC*

Register	Relationship	
	Significance level	Chi-2
Social register (criminal)— Temperance register	**	108.32
Criminal register— Temperance register		88.22
Mental register— Temperance register	n.s.	0.04
Criminal register— Social register (criminal)	**	100.32
Mental register— Social register (criminal)	n.s.	0.03
Mental register— Criminal register	n.s.	0.14

write, and who was discharged after one visit, as admitted to a psychiatric clinic for care in 964 where she remained for 4 months and, finally a boy a late developer whose immediate problem was that he was not mature enough to cope with school and who later developed a number of anti-social symptoms and other symptoms. One of these cases had been diagnosed as psychotic at the time of their discharge from the CGC.

Some typical cases who had been diagnosed as psychotic either while they were active cases at the CGC or later during the observation period, *are reported briefly as case-histories in supple*ment 3 (page 60).

Although the number of diagnoses of psychosis was practically even in all the age groups for the boys, there was a numerical increase for the girls from 0.5 % for the youngest group to 6 9 % for the oldest group.

The diagnosis of neuroses showed a similar distribution being more or less the same for the different age groups with respect to the boys but showing an increase for the girls from about 7 % in the youngest group to about 22 % for the oldest group ($p < 0.001$)

The treatment period needed by the in-patients was less than 6 months in the majority of cases but 0 3 % of all the boys and 0.8 % of all the girls had had to be hospitalized for more than 24 months during the observation period

Relationship between the various registers

Many of the cases who had been discharged during the years 1953–1954–1955 were to be found registered in several official registers by the end of the observation period. Table 12 presents relationship calculations between the different registers with reference to the boys in the material. Calculations of register relationships for the girls were not possible as the number of girls was so few As there was no similarity between the age distributions for the different groups (the mean age for those entered in the mental register was lower than that for the other registers, see also page 45 Chapter 7) the relationship calculations given in Table 12 refer to boys of corresponding ages (cases whose ages were between 6 6–11.5 years at the time they were discharged from the CGC). However the same relationships and levels of significance were obtained in the older groups also

It can be seen from the table that there is a highly significant relationship between the Social Register (criminal offences), and Temperance Board Register and the Register of Criminal Offences, whereas no significance can be found for the relationship between the Mental Register and either the Social Register or the Temperance Board Register or the Register of Criminal *Offences.*

Discussion

By means of searches of the registers in question, it was possible to trace 2 268 or about 96 % of the patients who originally numbered 2 364 in the material covered by the CGC during the years 1953–1954–1955 The discrepancy was therefore small and did not affect the results in any decisive manner Nor could this discrepancy be regarded as representing a highly specific selection of cases. The individuals concerned were a few who had emigrated, a few who had died during the observation period, and a few whose case-histories were incomplete. Mortality during the observation period was as could be

expected with respect to the age and sex distribution of the poulation (Larsson 1965).

A remarkably large number of the patients had applied for psychiatric care during the 10-year observation period, or had committed some offence against society that had led to some form of intervention by the authorities. In all instances, regardless of whether the matter was concerned with mental disorders or with crime the trend showed a continuous increase the cumulative frequency of cases applying for care or who had been registered in the register for anti-social offences showed a steady rise The implication of this is that the frequencies given represent minimum values which will continue to increase with extended observation periods. By extending the length of the observation period, it should be possible to show when the curve tapers off and flattens out.

The present authors felt it to be of considerable interest to confirm the absence of any statistical relationship between the group consisting of cases applying for mental care during the observation and the groups behaving contrary to the norms of society these groups being strongly correlated to each other It was more in keeping with our expectations to find differences between the sexes in the asocial groups, the boys being massively predominant in relation to the girls—this was not so in the case of those who applied for psychiatric care during the observation period, for this category the frequency for the boys was the same as the frequency for the girls.

Thus, the cases that were entered in the asociality register during the observation period were chiefly boys. For the few cases of girls in this category the debut usually took place at a later age than for the boys and the actual offence was less severe With respect to the boys, the risk of being entered in the asociality register was relatively low for children who were under the age of 10 years when they were discharged from the CGC, but from the age of 10 upwards this risk appears to be equally great for all ages (cf Dahl 1965).

The boys who were entered in the Temperance Board Register during the observation period comprised about 13 % of the total number of boys in the material. For the patients who were in the 11 6–15.5 years age group at discharge, the corresponding frequency amounted to about 23 % or practically every fourth boy This latter figure is lower than the frequency for Swedish boys, registered in the Temperance Board Register who had been followed up and who had attempted suicide (Otto 1971) but higher than the corresponding frequency for the individuals comprising the control group for the attempted suicide category these frequencies being 49 % and 13 %, respectively The figure in question is also higher than the frequency for boys entered in the Temperance Board Register and who were kept under long-term observation as the children of alcoholic parents, and the frequency for the corresponding control group the frequencies were 15 % and 7 %, respectively (Rydelius 1975). Another comparative group consisted of 222 randomly chosen boys from Stockholm between the ages of 8 and 16 years (Jonsson & Kälvesten 1975), and for this group the frequency was found to be 19 %. It should be added here that the observation period for all of these comparative groups was longer than that applied to the CGC patient material, and that the age of the clientele was higher

Registrations for criminal offences in the Social Register and in the Register of Criminal Offences made during the observation period accounted for about 21 % and, respectively about 12 % of all the boys in the material. The total (both registers) amounted to approximately 25 % of all the boys, or every fourth boy thus being registered for criminality The highest frequency of criminality around 36 %, was found for the age group between 11 6–15.5 years at the time of discharge from the CGC. In this connection, it can be mentioned that about 39 % of the suicidal boys mentioned above had been registered in the Register of Criminal Offences, while the figure for their control group amounted to 8 %. The corresponding figures for the children of alcoholic parents and their control group were 20 and 8 %, respectively Among the 222

boys from Stockholm who had been the subject of a follow-up study this figure was about 15 %. In the case of the criminalized boys comprising the clientele in the study by Ahnsjö (1973), about three-quarters of the total reverted to crime during the observation period

About 13 % of the boys who were inducted into the armed forces were released from compulsory military service owing to reasons associated with their mental health state According to the reg istration statistics kept by the Recruitment and Replacement Office of the Swedish Armed Forces, about 5 % of all recruits tested had been released on the grounds of the psychiatric diagnosis by the end of the 1960's.

Almost one-third of the total clientele, or approximately 32 %, boys as much as girls, had contacted some psychiatric institution during the llow up period. The figure for the girls who belonged to the highest age group at the time of their discharge from the CGC was as high as 43 %. Approximately 19 % of these had later been admitted to an adult psychiatric department for treatment. As mentioned above, the cumulative frequency for boys who had applied for psychiatric treatment during the 10-year period was about the same as the corresponding frequency for girls. If the frequencies of applicants are placed in relation to the age of the applicant at the time of discharge, the relationship found gives a different picture. In the case of the boys, this frequency fell steadily with increasing age In the case of the girls, the trend was quite the opposite. The reason for this may be that mental insufficiency in boys takes the form of asocial behaviour as they grow older which results in the community applying social measures rather than psychiatric measures, while girls who have a small-to-moderate need of psychiatric help in their early years have an increased need as they grow older but do not develop asociality as an expression of mental insufficiency

In recent years, a great deal of discussion has been devoted to the relationship between mental illness in childhood and in adulthood (see Rutter 1972). In the present study it is apparent that the girls in the child psychiatric clientele subsequently apply for adult psychiatric help to a far greater extent than the boys. In relation to the total need for adult psychiatric treatment however the addition of patients who had received treatment as children is extremely small. An even smaller number who had been diagnosed as psychotic in childhood received treatment for the same diagnosis during adult hood. A very few cases who had been in contact with the CGC when they were children for un characteristic nervous symptoms displayed a psychotic picture when they became adults.

CHAPTER 7 RELATIONSHIPS BETWEEN CERTAIN INVESTIGATION DATA FROM THE YEARS 1953–1954–1955 AND REGISTER NOTATIONS MADE DURING THE OBSERVATION PERIOD

As reported in the aforegoing chapter a large number of cases had been registered during the observation period in the Mental Register the Social Welfare Register the Temperance Board Register and the Register of Criminal Offences for reasons such as mental insufficiency charges of drunkenness or criminal offences.

At the conclusion of the observation period, 1 102 cases or approximately 49 % out of the original 2 268 cases in the material, had been entered in one or other of these registers. Out of the total number of 1 477 boys, 795 or about 54 % were registered, and out of the total of 791 girls, 307 or about 39 % were registered. The difference between the sexes is statistically highly significant.

The age distribution for the different groups—those not registered, those with notations in the

Social Welfare Register for criminality in the Temperence Board Register and in the Register of Criminal Offences—varies within and between the groups, as mentioned earlier

It can be seen from Table 13 that the age distribution is more or less the same for those individuals who did not have records in the registers as for those who were registered in the Mental Register The groups with notations in the Temperance Board Register and in the Register of Criminal Offences, both with similar age distributions, had a smaller number of individuals in the lowest age group (the majority of these had not reached legal age by the end of the observation period). This also applied to those with notations for criminality in the Social Welfare Register at the conclusion of the observation period, although in this case the difference was not as great.

In order to find out whether the data obtained in the course of the study of the years 1953–1954–1955 had any relationship with the registrations made in the official registers during the observation period, a comparison was made of all the data entered on the statistics sheet and statistically treated, with the exception of information pertaining to treatment (see below) in five groups

- — cases with no records of registrations during the observation period,
- — cases registered in the Mental Register
- — cases registered in the Register of Criminal Offences,
- — cases registered in the Social Welfare Register (criminal offences),
- — cases registered in the Temperance Board Register

As only a few girls had notations in the asociality registers (criminal offences, social welfare and temperance board), statistical comparisons between the girls were only possible with respect to girls with no records and girls registered in the Mental Register Concerning the girls, it was found that various items of data from the case histories and from the study were registered to more or less the same frequential extent for those who had no records as for those with notations in the Mental Register The comparison applied to the total number of cases in the respective groups since the age distribution for the different groups was the same

Table 13 *Age distribution among the boys, the material being presented according to notations in the different registers*

Register	Age at discharge –6.5 (%)	6.6–11.5 (%)	11.6–15.5 (%)	15.6– (%)
N record	24	40	25	11
Mental register	21	45	21	12
Social register	10	48	37	5
Temperance register	2	41	46	11
Criminal register	—	38	47	16

The relationships found for the boys differed from those applying to the girls. Because of the variations in the age distributions in the groups, the comparisons were based on groups that were matched age-wise that is to say on the boys who were in the 6.6–11.5 years age group at the time they were discharged from the CGC However the differences and the levels of significance were the same even in the older age groups.

Table 14 shows the differences for certain terms of data from the study with respect to the different groups. Only data occurring with statistically ascertained higher frequencies in one group in comparison to another has been included in the table.

The table shows that if a comparison is made between the cases that were not registered and the cases that were registered in the mental register there are significant differences relating to whether the patient lived with a single mother whether he had experienced the divorce of his parents, whether he had applied for help for hyperactivity whether his behaviour in school had been considered disruptive or whether he had been charged with pilfering or shoplifting. The greatest significance was found for those who had been brought up by a single mother

A comparison of the unregistered cases with those who had notations in the criminal register

Table 14. Frequential differences for various information derived from the 1953–1954–1955 study

The subjects are boys, grouped according to five classifications: (A) cases not registered during the observation period; (B) cases recorded in the Mental Register; (C) cases recorded in the Criminal Register; (D) cases recorded in the Social Register for Criminality and (E) cases recorded in the Temperance Register

Data from study	Diff A B		Diff A–C		Diff A–D		Diff A–E	
	Chi 2	Sign.	Chi 2	Sign.	Chi 2	Sign.	Chi 2	Sign.
Illegitimacy	2.96	n.s.	16.36		4_4		11.8	
Stepchildren	1.61	n.s.	8.10		6.14		3.81	n.s.
Single mothers	20.29		10.47		15.72	***	15.36	
Divorced parents	6.70		10.33		11.26	***	13.26	**
Working mothers	6.49		1.00	n.s.	5.44		7.77	
Social class 3	0.01	n.s.	11.68		14.00	**	13.80	**
Alcoholic father/mother	5.48		7.65		8.79		11.83	**
Psychomotor unrestic	8.53		9.44		2.67	n.s.	4.23	
Aggressiveness	3.13	n.s.	1.82	n.s.	7.45		8.45	
School fatigue	0.01	n.s.	1.72	n.s.	10.44		1.38	n.s.
Disruptive behaviour at school	6.95		36.51		23.88	**	36.87	**
Inability to follow tuition	0.19	n.s.	5.07		7.21		1.82	n.s.
Unconcentrated	2.88	n.s.	11.60		9.56		7.30	
fering/shoplifting	6.74		35.13		38.37		37.31	
behavioural orders	0.57	n.s.	13.21		14.84		5.18	

gave significant differences for several of the items of data from the study years. In particular: illegitimacy stepchild single mother and divorced parents, social class 3 alcoholic father or mother hyperactivity disruptive behaviour in school unconcentrated pilfering and shoplifting and a diagnosis of behavioural disorders.

Those children who had been registered in the social register for child criminality were also found to differ in several respects from the unregistered boys single mother divorced parents, social class 3 alcoholic father or mother aggressiveness, school fatigue disruptive behaviour in school inability to follw tuition, unconcentrated pilfering and shoplifting, and a diagnosis of behavioural disorders.

Finally with respect to the boys with notations in the temperance register these differed from the unregistered boys regarding the following items of data illegitimacy single mothers, divorced parents, working mothers, social class 3 alcoholic father or mother aggressiveness, disruptive behaviour in school unconcentrated and pilfering and shoplifting.

If a study is made of each item of data in the different groups, it is seen that the frequential differences for upbringing by a single mother parents divorce, disruptive behaviour in school and pilfering are significantly more common among the registered cases than among the unregistered boys. Certain symptoms occurring with greater frequential significance in the antisocial behaviour register than among the unregistered boys, do not occur with any greater frequency in those who are registered in the mental register illegitimacy social class 3 alcoholic fathers or mothers, unconcentrated or behavioural disorders.

Data that are usually assumed to be an expression of or indicate a predisposition for mental disorders—hereditary case history of mental disease, disharmonious marriage neurotic father or mother delayed development, enuresis, enkopresis, headaches, abdominal colic, tics, refusal to eat insomnia, obstinacy school fatigue difficulties in learning to read and write problematic personal relationships and diagnoses of neurosis and developmental disorders—occur to the same extent in the boys who are not registered as in those who are

Discussion

It is apparent from the above account that certain items of data, derived from the years of the study 1953–1954–1955, occur significantly more often among those patients who required mental care or who had been registered in the Asociality Register during the observation period. No single biasing factor or symptom occurred significantly more often amongst those who had not been registered in any of the registers by the end of the observation period. Five items of data were noted as occurring significantly more often among the boys applying for mental care as compared to the unregistered boys, one of these items showing a highly significant difference. 11 items occurred with significantly greater frequency among those registered in the Social Register and in the Criminal Register as compared to the unregistered boys, 6 of the differences being highly significant, and 10 symptoms occurred with significantly greater frequency among those registered in the Temperance Register as compared to those who were not registered, 7 of the differences being highly significant.

Four items were overrepresented in all of the register groups: upbringing by a single mother, divorced parents, disruptive behaviour in school and pilfering.

Other items were overrepresented only among those who were registered in the Asociality Register: illegitimacy, social class 3, alcoholic father or mother, the symptom of lacking in concentration, and the diagnosis of behavioural disorders.

Items such as neurotic parents, disharmonious marriage, symptoms such as enuresis and encopresis, psychosomatic symptoms such as headaches, abdominal colic and tics, refusal to eat, insomnia, obstinacy, school fatigue and problematic personal relationships, as well as the diagnosis of neurosis, did not occur more often among the registered cases than among those who were not registered.

Regarding the girls in the study, comparisons could only be made between the group containing cases needing psychiatric help during the observation period and the group consisting of those who had not been registered at all (because no statistical treatment was possible owing to the small number of girls with notations in the asociality register). In this case, it was found that there were no significant differences between the groups for any particular item of data from the years of the study 1953–1954–1955.

In summarizing, it can thus be said that, with respect to the boys, certain items of data constitute biasing factors for all of those who "slipped up" during the observation period, regardless of the nature of the slip-up, while other items, chiefly of a sociopsychological nature, constitute biasing factors only for those who were registered in the Asociality Register. Particular items that are usually associated with or represent neuroses do not appear to have been indicative of a poor prognosis for the observation period in question. The results presented are in good agreement with information published previously (Dahl 1965, Robins 1966, Sundby & Kreyberg 1968, King & Pittman 1969, Rutter 1972, and Ahnsjö 1973). It was not possible to establish the existence of similar relationships for the girls in the study.

CHAPTER 8. COMPREHENSIVE DISCUSSION

In the introduction to this report, the purpose of the study was summarized in question form, the two questions posed being:

1. What will happen to our patients in the coming years. How many of them will be in need of continued psychiatric care after being discharged from the child psychiatric clinics? How many will be in need of supportive measures from the community? How many will in time be in contact with the temperance and the law enforcement authorities.

2. Is it possible to predict, on the basis of t

investigation technique and the working methods that are used daily in child psychiatric care and from the information given by these procedures, which of our patients are likely to be in need of psychiatric and social care facilities?

This report presents the results of a 10-year follow up study of the patients who were discharged during the years 1953–1955 from the child guidance clinics (CGC) functioning under the auspices of the City of Stockholm Authorities.

A future report will present the results of a continuation of the present study covering the subsequent 10 years. In view of this coming report and with respect to the age distribution of the subjects in the present report—the youngest age groups had not yet reached adulthood by the end of the 10-year observation period—the material presented here has not been subjected to comprehensive and in-depth penetration. owever work on these details is planned in ion with the completion of the 20-year low-up observation period The authors have nevertheless found it to be expedient to present at the present time the patient material and the follow up results from the first period of 10 years, together with some simple calculations pertaining to relationships between certain data.

The trial material comprised 2 364 patients, whose ages ranged from 0 years up to 20 years.

In the vast majority of the cases, the families had approached the CGC on their own initiative

Regarding social class level, the clientele did not deviate from the average population distribution in Stockholm according to the official statistics for the years in question.

The number of boys applying for help far exceeded the number of girls. This numerical difference was particularly pronounced during the school years. In the years after the age of compulsory schooling, the figures for boys and for girls were more or less the same

The symptoms for which help was needed were for the most part of a child neurotic" nature anxiety difficulties in personal relationships, habitual manipulations (thumb-sucking, nailbiting, etc.), obstinacy negativism, hyper activity tics, insomnia, and so forth. Symptoms of an anti-social nature were more rare as were grave psychopathological symptoms.

The symptomatic picture for the boys differed from that of the girls in that the boys more frequently showed symptoms such as hyper activity disruptive behaviour in school truancy pilfering, etc. In the girls, the dominating symptoms were those of depression, insomnia, refusal to eat and anxiety The boys in the material thus reacted predominantly with symptoms that undoubtedly caused disturbances in their surrounding environment—particularly while attending school—whereas the girls reacted more frequently with symptoms that were more di stressing to themselves than to others around them.

It can be assumed that it is just this propensity for behavioural reactions that are disturbing for the environment which is the reason why the boys constitute a greater portion of the clientele than the girls among the child psychiatric patients. It has been demonstrated (Sandels 1963) that girls are able to concentrate their attention on tasks and work together in groups at an earlier age than boys can with the result that the girls can adjust more smoothly to the school environment.

The tendency shown by the boys in our material to react in a disturbing manner is, of course, a common occurrence in boys generally in the school environment. At least, this can be said to be true for what is generally termed "western culture" Therefore one cannot make the assumption that our material contained a selection of particularly difficult or disturbed or deviating boys.

Furthermore, only a very few cases were diagnosed as character disorder psychotic or gravely handicapped from some other cause It should however be noted that some of the diagnoses were probably not stated in full for cases of this type in the CGC material. The reason for this is the caution usually exercised in actually labelling a serious diagnosis in view of the consequences this might entail for the patient.

It can thus be established that the patient material upon which this report is based does not appear initially to be particularly seriously biased, judging from the case histories and the results of the studies. Cases that were found to be socially deteriorated and that were treated during the observation period by the CGC by means of the facilities offered by the Social Welfare Medical Officer or the childrens institutions, were not included in the present trial material—as was mentioned in an earlier section of this report. This should be borne in mind when discussing the results presented here

An assessment of the results of the therapeutic measures applied on behalf of the families involved during the years 1953–1955 has not been considered feasible in this connection, for several reasons. Obviously in selecting the children and families that were to be the subjects of psychotherapeutic measures of greater intensity than was normal at that time the choice was deliberate. Thus, no comparative material is available which comprises an adequate number of untreated cases. In addition, an evaluation of the treatment results at such a late stage would require a very time-consuming methodology of quite a different type than that used in this study involving personal interviews, different assessment and evaluation scales, and so forth

In order to provide an answer to the first of the questions posed above—what will happen to our patients in the coming years—each separate case was followed up during the ten years subsequent to their discharge from the register in which their case had been entered A relatively small number of "drop-outs" could be accounted for Mortality during the follow-up period was no higher than that of the normal population with respect to the age and sex distribution of the material

In the course of the follow-up study it was found that totally more than half the number of boys and more than one-third of the number of girls had applied for psychiatric care (child or adult psychiatric care as either in- or outpatients) during the 10-year follow-up period or were registered in the asociality registers (= child criminality in the Social Welfare Register the Temperance Register or the Criminal Offences Register)

As each patient was followed up for only 10 years after discharge, and as the cumulative frequencies show a continuous upward rise, it is highly probable that these figures will rise even further particularly as the children who were at the pre-school age during the follow-up period had not yet reached adulthood

The 20-year follow-up study that has been planned certainly appears to be of considerable importance in order to clarify whether certain disorders and background factors present during the more formable early years can provide prognostic information of value, using the methodological techniques applied in this study

Taking into account the fact that so many of the patients who were discharged during the years 1953–1955 continued to be in need of help in some form or other there is every reason to ask whether this is indicative of poor therapy results. As we have already pointed out, the present report cannot supply answers to questions of this type.

Thus, we do not know how many families would have experienced even worse troubles and problems if we had not been able to give them such help as we could at that time The fact that a family who had a positive experience of help provided by a mental care unit on one occasion applied for renewed help from that unit or from an adult psychiatric department at a later date in order to be able to cope with a relapse or a crisis, need not necessarily be regarded as a poor therapeutic result.

It is obviously not possible to offer a similar explanation with respect to the boys who were entered, in increasing numbers, in the various registers for asocial behaviour during the period Nevertheless, a single registration in one or other of these "anti-social registers" should not be given too much importance

As reported above pronounced sex-associated differences were present in the material right from the very beginning. Boys applied for help from the CGC at an earlier age and with greater

frequency than the girls, and also displayed a symptomatic panorama that differed from that of the girls, averagely speaking.

Even more pronounced differences appeared during the 10-year follow-up period

Whereas the boys were overwhelmingly predominant with respect to entries in the "anti-social registers" the girls showed a steady increase in the number of individuals requiring psychiatric care Although both sexes were registered with equal frequency percentage-wise in the Mental Register during the period the frequency for the boys was greater for the younger age groups (and were consequently registered in the child psychiatric register) while the girls showed a trend in the opposite direction with a curve rising progressively with age (and thus dominating in the adult psychiatric register). No explanation can be given for this sex difference

The differences in reaction patterns for boys girls, as described above can nevertheless be assumed to play an important role As mentioned earlier the mode of reaction displayed by boys is more disturbing, even at the pre-school stage, to the environment than that of girls, and consequently applications for psychiatric help for boys are made more frequently than in the case of girls.

This tendency culminates during the school years. In this connection it might be of interest to make a comparison with the report by Emanuelsson, entitled "A long-term perspective of educational handicap" (1974) The author confirms that certain early educational handicaps (low IQ and low social status) are most probably complicated and compounded by experiences during school-age and emphasizes particularly the importance of the first years at school for this depressing course of development.

The predominance of boys in the school-age clientele might indicate that even other types of early "educational handicaps" other than those studied by Emanuelsson can become fixed and amplified during the school years According to Emanuelsson, the school reform instigated in recent years in Sweden have done nothing to alter this state of affairs.

The efforts made by the CGC in the form of therapy nursery schools and therapy schools, and different forms of collaborative work with the schools, can therefore be regarded as important but insufficient attempts to counteract this development trend

A few of the patients among those who had been discharged from the CGC during the years 1953–1955 had been diagnosed as psychotic cases at their primary examinations, the symptoms being autism, no contact with reality delayed speech development stereotypy etc. Without exception, these cases all required long-term institutional treatment during the years covered by the observation period

A few patients who had been suffering from uncharacteristic nervous symptoms at the time they applied for help from the CGC, were diagnosed during the subsequent observation period as suffering from schizophrenia or respectively manodepressive psychosis In none of these cases did the picture of psychosis emerge before puberty This is in good agreement with previous findings (Rutter 1972)

The patients who were diagnosed as neurotic at the time of their examination at the CGC were found to have good prospects insofar as they were not overrepresented in any of the registers in question and that only a few of them turned up again under the diagnosis of neurosis in the adult psychiatric register Even this finding agrees well with earlier findings (see literature survey).

In order to throw light onto the second of the questions posed earlier—whether it is possible to predict, on the basis of the sum of the information obtained from child psychiatric sources and from the investigation techniques used which of the patients are likely to be in need of psychiatric and social care facilities—a study has been made of the relationships existing between data obtained from the initial examinations at the CGC during the years 1953–1955 and notations entered in the various official registers during the subsequent 10-year follow up period

Even here circumstances relating to boys differ from those applying to girls

Thus, the frequency value for boys living with only a maternal parent was high and strongly significant for those who required psychiatric care and for those who had records in the asociality registers.

The boys who had been registered in the asociality registers during the observation period came predominantly from social class 3 homes, in comparison with those boys who had not been registered at all. Furthermore the registered boys showed that a higher percentage of them were illegitimate, they had more often grown up in homes where the father or the mother was an addict, they had more often displayed symptoms such as pilfering, truancy disruptive behaviour in school, etc., and had more often received a diagnosis of behavioural disorder All of these circumstances are well-known from earlier investigations.

As only a very few of the girls in the study has been registered in one or other of the asociality registers, a comparison could only be made between those who were not registered at all and those who had applied for psychiatric care during the observation period. The comparison showed that data deriving from the initial examinations appeared to more or less the same extent for both groups.

Strangely enough, there was no evidence that a greater number of children came from homes with "mentally sick" or "neurotically insufficient" parents or from homes where the parents marriage was "disharmonious" among those who later required mental care or who were registered in the asociality registers in comparison to the children who were not registered at all during the observation period.

In summarizing, it can be said that, in the case of the boys, certain recorded background factors of a sociological and psychological nature in combination with a special reaction pattern give some indication of a risk of asocial development, but are hardly indicative of a risk of future psychiatric complications.

In the case of the girls, the factors recorded did not provide any information of this nature which would enable any predictions as to the future to be made

The type of sex-associated differences discussed in the aforegoing have been discussed by other authors, e g. Cowie et al 1968, who felt that boys exhibited a far greater degree of sensitivity than girls in their way of reacting by displaying anti-social symptoms. Circumstances would have to be much more serious for a girl to react with the same degree of asociality as a boy Rutter (1970) states that mental disturbances in girls appear to be due to genetic factors rather more often than in the case of boys, whereas the boys would react with a greater depth of emotion to conflicts in the family

The differences in reaction patterns between boys and girls established in the present report—which can, of course, be governed by the constitutional make-up of the individual to a greater or lesser degree—might indicate that the reactions displayed by girls in the face of environmental stress factors follow a pattern which outwardly appears to be less emphatic than the symptoms displayed by the boys but which, with increasing age leads to a progressively greater need of psychiatric care, as noted for the girls in our material.

When it comes to predicting psychiatric complications for boys and girls, the background factors and their statistical treatment do not offer any help. It is possible that a more detailed study employing a technique that can deal with disorders and complications—in relation to the individual and to the family relationships—in a more satisfactory manner might be able to provide us with improved prognostic information applicable to these cases. This assumption is supported by the results obtained from a study carried out in 1956 of a clientele consisting of young criminals, in which a combination of projective test methods designed to provide pointers for asociality was used with considerable success (Humble, Settergren 1974).

A similar method, adjusted to trace cases harbouring a psychiatric risk, is a fully feasible possibility that falls within the scope of the CGC facilities

One of the essential results of the present study is that it shows quite clearly that the CGC clientele contains a large number of children who will be needing help and support from the community for a very long time ahead This applies to the boys who act out their reactions and who will later become progressively involved in more and more serious conflicts with the norms of society and acquiring an ever increasing burden of charges and registrations because of alcoholism and criminal offences, and also to the children and young people who will later become increasingly handicapped by mental trouble and psychiatric illness. There is no doubt that the investment of resources in prophylactic measures in the fields covered by both these categories is a matter of extreme urgency with respect to both the humanitarian and the economic aspects involved

A prerequisite for effective prophylatic measures is the possibility of being able to detect, at the earliest possible stage and with far greater certainty than has been accessible to us so far children who are in the risk zone and providing them with the necessary treatment This can best be achieved by expanding research in breadth and in depth in the fields in question

CHAPTER 9 SUMMARY

hapter 1

here is a tremendous call for clinical research in the field of child psychiatry Even today there is considerable uncertainty as to the long-term prognoses for those patients who seek help from the child and youth guidance clinics, and the factors responsible for permanenting nervous disorders and difficulties in adjustment The questions for which the authors require answers are How many of the patients visiting the Child and Youth Guidance Clinics will later be in need of psychiatric care? How many will experience problems in social adjustment at some future time? Is it possible to foresee or anticipate the future path of a patient on the grounds of the information acquired from routine examinations performed in child and youth psychiatric cases?

The chapter also includes a survey of the most important studies dealing with these questions and similar problems.

Chapters 2 and 3

These chapters present a historical review of the open-care psychiatric clinics for children in Stockholm, from the initiation of the institution in 1933 up to the present time Basic evaluations and principles are discussed and summarized in a fundamental psychological–sociological concept Descriptions are given of problematic aspects, target groups, methods of approach and resources. The authors concentrate particularly on the conditions prevailing at the Child and Youth Guidance Clinics during the period 1953–1955 which represents the pertinent investigation years. During the course of the study a number of factors concerning each patient and his/her environment were recorded on a standardized statistics sheet at the time of examination and during treatment. The team of doctors, psychologists and social workers responsible for the patient entered this information on the sheet and it was further checked regularly during the observation period by one and the same psychologist Obvious errors in registration were corrected. The data thus acquired constituted the material on which the description of the patients, the findings of the examinations and the results of the treatment were based.

Ten years after the patients had been discharged from the Child and Youth Guidance Clinics, they were traced through the population census register and parish records offices. They were then checked against the records of the social welfare and temperance boards, the Crimi

nal Deliquency Board, the Recruiting and Replacement Office of the Swedish Armed Forces, and in all the hospital registers in the districts where the patients had lived. By this means it was possible to obtain information as to whether the patient had required psychiatric care and/or whether they had been subjected to registration by the authorities for asocial behaviour during the observation period

The material was computerized. Conventional statistical calculations were employed.

Chapter 4

The patient material comprised a total of 2 364 individuals, 145 of whom being on the active case list on repeated occasions during the investigation period The actual number of reports therefore totalled 2 509 In relation to the population figures for children and young people, the largest number of applicants for care at the Guidance Clinics was to be found in the age-group 6.6–11.5 years this applied to both boys and girls. In the pre-school age-group, the incidence of boys was higher than that of girls and much higher during the school years, after school age the incidence was the same for boys and girls. A comparison of the patient material from 1953–1955 with patient material from 1970 shows that a shift towards the upper age levels has taken place particularly with regard to the girls.

The social-class distribution of the material corresponds to that of married male voters in Stockholm for the same period

In 77% of the cases, the patients came from complete homes while 20 came from homes with only the maternal parent. Every tenth child was a stepchild a few were adopted. 12 of the children were illegitimate and 1% had experienced a divorce situation. In 27 of the cases, the mother went out to work.

Concerning the parents, 4 of the fathers and 4 of the mothers were mentally ill, 8 of the fathers and 16 of the mothers were neurotically disturbed, and 7 % of the fathers were addicts (alcohol or narcotics). The marriage was stated to be "disharmonious" in 14 % of the cases.

Chapter 5

This chapter accounts for the data obtained from the investigation covering the years 1953–1954–1955.

In the majority of cases, approximately 85%, the parents or the patient took the initiative in contacting the clinic, 6 % were sent through the schools and 4 through the Child Welfare Board

For more than 10% of the cases, the symptoms and adjustment difficulties necessitating the contact with the Child and Youth Guidance Clinics were as follows developmental abnormalities, enuresis, tics, refusal to eat, sleep disturbances, speech disturbances, habitual manipulations (nailbiting, thumb-sucking etc.) difficulties in making and maintaining contact, mother fixation, hyperactivity school fatigue, obstinacy and aggressiveness, problems at school, and pilfering and shoplifting. Certain symptoms were more common among boys than among girls enuresis, encopresis, tics, speech disturbances, hyperactivity truancy problems at school, pilfering or theft. Others were more prevalent among girls depression and sleep disturbances. Some symptoms occurred with equal frequency in both boys and girls. Some symptoms diminished in frequency with increasing age enuresis, encopresis, refusal to eat, speech disturbances, habitual manipulation, hyperactivity other symptoms became more frequent depression, story-telling, attempted suicides, problems at school, vagabondage and running away and pilfering.

If the symptomatic picture presented by the study material is compared with the picture found for the patient material from 1970, it can be seen that the symptoms noted as being more common among the older children occurred with greater frequency in the more recent material.

Development tests or intelligence tests were used in 85% of the cases, 6% being tested according to Terman-Merrill The distribution of the test results in the test population was normal. Projective studies were also employed play investigation being carried out in 39% of the cases and 30% being given Rorschach tests.

and continued in trade school. Considered to be mentally weak (IQ 77 according to Terman-Merrill) otherwise unremarkable Sex education recommended. Discharged after visit to doctor 1955

Temperance Board Register

1957 Charged with drunkenness.
1959 Charged with drunkenness.
1960 Charged with drunkenness.
1961 Charged with drunkenness.
1962 Three charges of drunkenness.
1963 One charge of drunkenness.
1965 Three charges of drunkenness, and other crimes.

Taken in charge at a mental hospital in accordance with the laws pertaining to mentally decapacitated persons.

ase histories of three patients who were registered in the *Social Welfare Board Register* during the observation period.

Boy born 1948 Reported in 1953 on the grounds of fear of the night, bed-wetting and masturbation. Destructive, "broke windows" Illegitimate, no contact with father who has been convicted. Placed in home for infants after a short time with his mother Later placed in foster homes and then a Children s Home. Mother married in 1951 and took final charge of the boy Stepfather "strict" uses physical punishment on child (according to mother) Normal development physically healthy Mentally the child is anxious, unstable and aggressive. Good intelligence but "immature" IQ 147 according to Terman-Merrill Continuous supportive contact with mother–stepfather–patient Discharged after 1 year

Reported again in 1961 on the grounds of anti-social behaviour and considerable difficulties at school At that time relations between the mother and stepfather were very poor and they separated in 1963 Sporadic contact up to 1963 when therapeutic talks were resumed. Diagnosis character disorder? Unfavourable relationship with stepfather?

Social Welfare Board Register

1961 Damage to property breaking in. Probation.
1962 Theft of moped shop-breaking. Continued probation.
1963 Theft on several occasions, breaking in. *Not convicted.*

Continued criminal behaviour and placed in reform school.

Boy born 1948 Reported in 1954 on the grounds of excessive hyperactivity and aggressiveness. Single mother Lived at home for single mothers for 5 months, and later at home for infants. Subsequently in charge of the mother until 2 years of age, followed by 1 year in foster home Returned to mother and lived with her at institution, still there to date. Mother in poor physical and mental condition, hospitalized for long periods, brought up in Home for Children, placed at times in institutions for socially maladjusted children Attempted suicide in 1954 *Patient physically healthy and previously showing normal development* Mentally always unstable, nervous, difficulties with friends. Vagabonding. Aggressive. Upon examination found to be physically healthy Mental state restless, unconcentrated, mentally weak. IQ 108 according to Terman Merrill. Found to be insecure Supportive contact with mother and child Group therapy with the patient Summer home for 2 months, patient s attitude afterwards said to be "calm and pleasant" Mother decides to let the boy remain at the summer home for a year Continues living there even afterwards.

Social Welfare Board Register

1962 Reported for pilfering. No conviction.
1963 Reported for pilfering. No conviction
1963 Reported for theft
1963 Reported for theft of motorbike.
1963 Reported for theft, illegal distilling and illegal driving. Later admitted to mental hospital for alcoholism.

Boy born 1946 Reported in 1953 on the grounds of aggressiveness, wilful damage arson and school problems. Complete home, 2nd of

three siblings. Mother suffering from depression, receiving psychiatric treatment. Disharmonious marriage. Patient placed in Home for Children as mother could not cope with him. Referred to the CGC by the Home. Child Welfare Committee arranged for boarding in foster home—similar arrangements for younger brother Returned to own home when mother was discharged from hospital. Mentally primitive few capabilities. IQ 83 according to Terman-Merrill. EEG general pathological activity no focus." Only sporadic contact with CGC and only when the Child Welfare Committee insisted. Discharged in 1955 without any special measures being taken.

Social Welfare Board Register

1955 Taken in charge owing to mother s depression.

1956 Taken in charge owing to pilfering, theft placed in Home for Boys. Sent to another Home for Boys later that year reason unknown.

1960 Foster home, which did not turn out well and he was returned to the Home for Boys later that year

1962 Again sent to Home for Boys, ran away sent to another (the 4th) Children s Home.

1963 Serious theft (snatching handbags), breaking and entering. Sent to reform school.

Case histories of three patients who were registered in the *Register of Criminal Offences* during the observation period.

Boy born 1944 Reported in 1953 on the grounds of aggressiveness and adjustment difficulties at school. Complete home, 2nd of three siblings. Father is an alcoholic, in contact with psychiatric clinic, has attempted suicide several times. Mother is worn-out and depressed. Pregnancy and partus normal. Development normal. Mentally always unstable and aggressive Did not become really problematic until he started school where he reacted to tight situations with violence, even attacking the teachers and headmaster The school felt unable to deal with him and requested immediate help. Boy examined physically normal and well developed Mentally unstable, uncontrolled, poor personal relationships. Rorschach test results "day-dreamer type The test does not indicate a more aggressive or explosive reaction pattern" IQ 89 according to Terman-Merrill. The school contacted the CGC during the course of the investigation "the class is scared stiff of the patient. Attacks with weapons" Placed in remedial class for observation. Physical examination, including EEG reveals nothing abnormal. Patient treated in "handicraft" therapy group, mother in "talks with mothers" therapy group, father declines participation. Continued and increasing maladjustment at school. Change of school in 1954 Group therapy at CGC continued. Father admitted concurrently to home for alcoholics. Patient commits wilful damage in 1955 Plays truant from school but mother states that "he behaves better now at school" and there are no problems with him at present" The boy tires of the therapy group and gives up attending. As a result, he is discharged from the CGC.

Register of Criminal Offences

1960 Serious thefts on several occasions, unlawful driving. Conviction Hard labour 1 year

1961 Unlawful dispossession of serious nature, unlawful driving. Conviction 6 months hard labour

1962 Assault and battery drunken driving. Conviction 3 months hard labour

1963 Serious unlawful dispossession. Conviction 3 months hard labour

1963 Wilful damage and serious unlawful dispossession. Conviction 3 months hard labour

1963 Unlawful driving, serious drunken driving. Conviction 6 months hard labour

Boy born 1941 Came to the knowledge of the CGC in 1951 after running away from home following a quarrel with some children of the same age Had played truant from school shortly before this incident. Complete family younger brother normal. Family circumstances stated to be normal. Mother's pregnancy and

partus normal. Development unremarkable, physically healthy Always showed lack of con centration and instability bad tempered, often quarreling and fighting with friends. Pilfered newspapers in 1951 reported to the Child Welfare Committee no measures taken Results of examination somatically normal. No somatic indications of puberty Mentally unconcentrated uneven performance, considered to be "emotionally disturbed" IQ 94 according to Terman-Merrill. The mother does not give cause for continued contact with the CGC and the case is therefore closed without any special measures being taken The mother again contacts the CGC in 1953 after the patient, together with some friends, has broken into the school and stolen various objects. He was discovered and questioned by a teacher When the father was told of the incident, he gave the boy a beating. The other states that the boy is frightened of ysical punishment. According to the school, the boy is "badly disturbed" and has previously stolen things from the school. The patient is placed in group therapy but stops attending. "No help from patient s family Case discharged (after 3 months contact). No subsequent contact between the patient and the CGC.

Register of Criminal Offences

1958 Serious theft on three occasions. Conviction 1 year imprisonment.

1959 Receiving stolen property Conviction 2 months imprisonment.

1960 Forging documents on 12 occasions, serious theft unlawful driving. Conviction juvenile prison.

1961 Charges as above. Conviction Hard labour for 2 years and 6 months.

1963 Illegal possession of drugs (narcotics), aggrevated unlawful driving, drunken driving, assault. Conviction 6 months imprisonment.

1964 Drunkenness and assault and battery Conviction Prison for habitual criminals.

Boy born 1940 Report in 1947 on the grounds of school immaturity Motherless since the age of 4 years. Several foster homes because the father was incapable of taking care of the boy Both parents severely socially maladjusted. Has remained in the same foster home for the past two years, where conditions are good according to the Child Welfare Committee Development unremarkable physically healthy Mentally "a hard type" says the foster mother Has difficulties with children of the same age, gives a general impression of "nervousness" Examination findings anxious, uncertain and generally immature. IQ 93 according to Terman-Merrill, steady test profile Discharged without special measures, except recommendation regarding schooling. Reported again in 1953 because of hyperactivity adjustment difficulties at school, and general "nervous symptoms" Mentally weak. Keeps company mostly with younger children. Afraid of the dark, has to sleep with foster mother Has started truancy Talks with foster mother on 4 occasions. Theft of moped in 1954 police report. Contact with the Child Welfare Committee, who pursues the case Discharged from CGC in 1954

Register of Criminal Offences

1957 Serious theft. Conviction Imprisonment for 1 year

1958 Serious theft Conviction Imprisonment for 3 months.

1959 Serious unlawful dispossession, serious theft, Conviction Juvenile prison.

1963 Serious theft, petty theft. Conviction Hard labour for 1 year and 6 months.

1964 Manslaughter Convicton 10 years imprisonment.

Examples of some *cases who were diagnosed under the heading of "Psychosis"* during the period of the CGC trial (1953–1954–1955) or during the subsequent 10-year observation period

Child psychoses

Girl born 1948 Reported in 1952 on the grounds of refusal to eat. Difficulties in personal relationships Mother died when patient was one year old, father remarried. No history of hereditary disease. Mother's pregnancy and partus

were normal. Placed in Infant's Home for the first 2 months after birth, followed by 4 months at home with parents, and then Children's Home until 1 year of age. Spent the next 2 years passing through 7 foster homes. Late developer, refuses to eat. Appears "vacuous", fearful, sits in a corner and sucks her fingers. Complete refusal to eat and must be fed forcibly. Started vomiting after feeding. Was found upon examination to be passive, "screened off", undeveloped. Talks "baby language". Development quotient 74 according to Bühler Hetzer but in several respect seems to be equivalent to her age. Admitted to child psychiatric department in 1952, after which her eating problems let up for a while, but revert when she is discharged. Nevertheless, appears to be calmer. Continuous contact with CGC. Placed in kindergarten (day care home) in 1953 and begins to make contact with other children. But still very reserved, acts on impulse (aggressive impulses), stereotypy. Spent the summer of 1953 in a summer home, after which she showed improvement. Intensive masturbation in 1955. Hospitalized at child psychiatric department where she is considered to be a case of child psychosis. She is recommended for admittance to a therapy home and is subsequently transferred. Discharged from the CGC in 1955. Later in 1965 she is admitted to an institution for easily managed psychotic children.

Girl, born 1936. Reported in 1955 in connection with application for invalid pension and advice concerning training. No history of hereditary disease. Parents divorced, father given guardianship, now remarried. The patient has lived with an aunt from the age of 3 years until the age of 7 years, when she went to live with her father and stepmother. The biological mother's pregnancy and partus was unremarkable, as was the patient's development. When the girl was 3 years old, she began to change: she became increasingly stiffer in her movements and tense, and withdrew. Victim of mobbing. Exceedingly sensitive. Between the ages of 6 and 8 years, she attended the Erica Foundation (private child guidance clinic in Stockholm) where she was considered to be schizophrenic. Started school in a normal class, transferred to remedial class in the 2nd year which led to such an improvement that she could later return to the normal classes. She left school with good marks. Could not manage a job after schooling. Passive, lacking initiative. Was granted a pension which is now the subject of renewal application. Upon examination, the girl was found to be "screened off", unable to make and maintain contact, showed stiff facial movements and spoke in an affected manner. Is tested and found to reach an IQ-level of 76 according to Terman-Merrill. Gives the impression of grave mental defectiveness which "corresponds in all essentials to schizophrenia". Recommendation placement in family care. Application for pension approved. Discharged from the CGC with the diagnosis of psychosis.

Re-examined at the psychiatric department in 1957: diagnosis schizophrenia.

Boy, born 1946. Reported in 1951 on the grounds of generalized late development. Mental illness on the mother's side. Both parents and younger sister physically healthy. Normal pregnancy and partus. Generally rather late in development, speech retardation in particular. "Stopped developing" from the age of 2 years. Severely withdrawn, sits by himself alone, wanders off, must be watched. Does not understand the necessity of being careful. Does not miss his mother if she leaves him alone. Stereotypy, laughs to himself. Inexplicable unbalanced outbreaks of temper which pass over quickly. No initiative. Upon examination, was found to be slow, circumstantial and irritable. Speech garbled but garrulous. Appears to be screened off, no involvement. No anxiety or open agitation. Development quotient 101 according to Bühler Hetzer. Continuous supportive contact with parents and patient. Admitted to child psychiatric department for hospitalization in 1952. Behaviour: withdrawn, assumes affectations at times, talks to himself and makes up new words. Building in sand-pit chaotic. IQ 101 according to Terman-Merrill. A diagnosis of schizophrenia was discussed but as his state improved during hospitalization, the diagnosis

given was Neurosis Schizoid. Continued contact with the CGC is recommended Started school in 1953 and copes "well" seems to be developing satisfactorily Discharged from the CGC in 1953 with a diagnosis of behavioural disorders.

Hospitalized in 1963 and 1965 (child psychiatric dept.) after attempted suicide on both occasions. The patient was found to exhibit "a clear picture of schizophrenia" with "magical and superior ideas"

Boy born 1952 Reported in 1954 on the grounds of restlessness, stereotypy delayed speech development. The parents married when the boy was born but their relations were not harmonious. Divorced in 1955 Mother depressed. Normal pregnancy and partus. Cried a lot as an infant, particularly at nights, but otherwise normal Started battering his head against ... already in infancy Excema from 1 month otherwise healthy Boarded at Home for from the age of 9–12 months owing to ...ther's illness. Underwent a mental change" after this visit stopped smiling and laughing, was restless and destructive withdrawn. Acted aggressively towards other children Admitted to child psychiatric department in 1955 Somatically normal Mentally "screened off" hyper active whiny Would not talk. Stereotypy Bühler Hetzer investigation gave development quotient = 91 Mother found to be mentally inadequate Recommendation of group therapy for the child and continuous supportive contact with the CGC for the mother put into effect. But as the boy's status does not improve he was placed in a therapy home in 1956, the clientele at the home being easily managed, mentally defective children. Contact is maintained with the mother through the CGC The boy improved during his stay at the therapy home but in 1959 an examination at the CGC shows that he still exhibits stereotypical actions, that he has difficulties with personal contacts but that he is interested in "things" When he speaks, he articulates well and can express himself with a vocabulary in advance of his years. He is discharged from the CGC following this examination as his mother is moving to another town in central Sweden and has obtained the release of the child from the Home so that he can live with her again Diagnosis Psychosis.

In 1960, the boy was admitted to the child psychiatric department at the hospital in his new home town, the reason being an investigation of his case in order to place him in a foster home He was found to be "a singular personality difficult to interpret" Talks nearly all the time perseveration tantrums. Talks about macabre things headless bodies, brain fluid the odour of uterus, etc. Never takes part in group play Often scribbles. Constantly sucking a bit of his shirt or tearing the material with his teeth. Constructed a "whipping machine" Intellectually he functions on a normal level.

Recommendation to be placed in a therapy home This is put into effect and he stayed at the Home until 1964

Diagnosis Infantile autism.

Boy born 1945 Reported in 1950 on the grounds of hyperactivity aggressiveness and problems in his contacts with children of the same age. Nothing of particular interest in his hereditary history Complete family The elder of two siblings, the brother being in full health. Spent 6 months boarded at a Children's Home when he was 2 years old while his mother was ill. He reacted by bedwetting and refusing to eat. After this visit, he spent three months with his maternal grandparents, and subsequently with an aunt until he was 5 years old He then returned to his own home. The mother's pregnancy and partus were normal. Development unremarkable until the age of 2 years, but remained static from then on No contact with other children. Examination showed withdrawal *talks to himself* appears deficient. Placed in play therapy does not respond. Daydreams, stereotypy perseveration. In 1952, a notation is made of his autistic behaviour Postponement of school start in 1952. Goes to play school but is badly mobbed, and becomes aggressive himself after a while. Although he shows some development, his "original" behaviour becomes more marked. He is registered with the

organisation for mentally deficient children and adults in 1953 but the parents manage to get him placed in a school remedial class. However this is a distinct failure It was suggested that he should be placed in a therapy home but a special school was decided upon instead. He was discharged from the CGC in 1953 but re registered again after only a short time He was given individual therapy in 1953 after an attempt at group therapy During the rest of 1953 and in 1954 the boy is calmer and attends school but shows a deterioration towards the end of this time, becoming increasingly withdrawn. He is referred to the child psychiatric department at the hospital but his admission is postponed until 1956. After being admitted to the hospital, he is found to show "a grave psychotic picture" with withdrawal, stereotypy perseveration, assumed aural hallucinations. He is considered to be suffering from endogenic psychosis and a therapy home is recommended. However in the Home he has "psychotic outbreaks" and is removed to an institution for difficult mentally and developmentally disturbed children.

Schizophrenic states

Girl born 1938 Reported in 1942 on the grounds of hyperactivity aggressiveness and affective instability New report in 1952 because of stepfather problem Father mentally ill. Complete home, only child. Normal pregnancy premature birth, incubator remained at hospital for 5 months. Development unremarkable. Hyperactive right from the beginning, "wore her mother out completely" For this reason was placed in a Children s Home at the age of 3 years for 14 days. At the home, she was listless and apathetic. The case was closed in 1942. A few visits had been made and on these occasions, advice had been given In 1952, the girl was having problems with her schooling, she was unconcentrated, "nervous" but obedient and pleasant" At home, she had tantrums. She was suspicious and aggressive towards her mother who had remarried Her relationship with her stepfather was good Spends a lot of time on her own. Upon examination was found to be tense, inhibited and having contact difficulties. IQ 108 according to Terman-Merrill. Fantasies about "dripping blood, madness, and the like" Rorschach "intense aggressiveness and strongly inhibited against it" Nothing indicative of schizophrenia

Continued supportive contact with the parents and the patient. Change of school recommended. Improvement. Is discharged in 1955 in connection with a trip abroad. Diagnosis Neurosis.

Reported again in 1955 because of "hysteroidal reactions" Obsessive thoughts, daydreams, self-reproaches. Unconcentrated and split. Attacks of anxiety which make her disorientated Forced to break off her studies at the College of Arts. After intensive and frequent contacts with the CGC, she is admitted to the psychiatric department for hospitalization. For this reason, she is discharged from the CGC with a diagnosis of psychosis. The diagnosis of the psychiatric department while she is under care is schizophrenia. Treatment with insulin shock and ECT Lively hallucinations during hospitalization period. Subsequently re-admitted to the psychiatric department on a number of occasions under a diagnosis of psychosis. During the years 1956–62, she is hospitalized for a total time of 2 years and 8 months. Full invalidity pension.

Girl, born 1936 Reported in 1953 on the grounds of contact difficulties. No hereditary history of mental disease. Complete home. The 4th of four siblings. Siblings normal Pregnancy and partus normal Development unremarkable. Physically healthy Always shy and reserved. When hospitalized at the age of 2 years, she "went completely stiff" but this passed after about 1 month Became more and more reserved from the age of 10 years onwards. During the last 6 months, felt that people were looking at her Was irritable when we tried to make contact with her suspicious. Delusions. Upon examination was found to be suffering from contact difficulties, was fragmented and spoke incoherently Debut for schizophrenia? Is transferred to the psychiatric department for hospitalization and thus discharged from the CGC in 1953. Reported again later the same year The hospital interprets her case as pubertal reaction in an

oligophrenic girl The CGC carried out a new examination. Rorschach suspected schizophrenia. Regular therapy with the patient but no noticeable improvement Still withdrawn, suspicious, isolated, indifferent to her parents. Attempt at training for trade fails. Is discharged from the CGC in 1954 in connection with readmittance to psychiatric department. CGC diagnosis psychosis.

During the years 1955–65 she is hospitalized for a total time of 2 years and 4 months.

Girl born 1935 Reported by the mother in 1941 and in 1953 on the grounds of aggressiveness. No hereditary history of mental disease Complete family The eldest of two children. The brother is healthy Pregnancy and partus normal. Development unremarkable From the age of 2 years, the patient is aggressive, excitable and noisy Picks her skin until she bleeds. Refuses to eat. The results of an examination do not indi-e any abnormal findings and her general in-gence level is considered to be normal. Case ork offered to the mother does not lead to any improvement and the recommendation of plac ing in a Children s Home is therefore made. A new report is registered at the CGC in 1953 on the grounds of psychotic symptoms. Behaves mute during the first period at school but later manages reasonably well. Has recently taken to isolating herself at home Finally completely apathetic. Attacks of anxiety Afraid of germs. Suspicious. Occasional tantrums. Emotionally indifferent. Is admitted to Mental Hospital and therefore discharged from the CGC under the diagnosis of psychosis.

Treated at a Mental Hospital for two periods during the years 1953–1955 the total time being 2 1/2 months. Diagnosis Psychosis. Full invalidity pension

Boy born 1942 Reported in 1953 on the grounds of bedwetting, hyperactivity and disturbing behaviour at school. No hereditary history Complete home Only child. Normal pregnancy and partus. Ordinary development. Physically healthy Mentally always aggressi e obstinate attached to mother Problems with friends. Troubl at school right from the start excitable, disturbing, aggressive towards classmates. Upon examination the boy is found to be tense "screened off" and sensitive, with a normal intelligence level. Physically normal. Is placed in group therapy but breaks off after a short time As a result, the case is closed in 1953 He is considered to be exhibiting mild environmental reac tions.

Hospitalized at a psychiatric department in 1961 1962 and 1963 for a total time of 9 months, with a diagnosis of psychosis. Is later admitted to a Mental Hospital as being in need of care

Boy born 1944 Reported in 1952 owing to obstinacy and sibling conflicts. No hereditary history Complete home, the 2nd of three siblings. The father is a melancholy man, the mother is a worrier The older sister is a bed-wetter The patient is at times affected with asthmatic trouble He has always been a "loner" does not make contact with other children easily Aggressive towards other children. Uses "baby language" at times, makes "grimaces" During the past year he has been acting aggressively towards his younger brother Troublesome at school but capable of meeting the demands of school work. Upon examination, he is found to be worried, slow and inhibited. Uneven performance. IQ 103 according to Terman-Merrill Report of psychological observation states that the boy is disharmonious and has difficulties in making and maintaining contacts. Continuous supportive contact with the CGC, but the boy remains unaffected. "Spiteful towards small children, tells lies, and refuses to go to school" (1953). Is placed in an observation class. Rorschach test results show a picture of a "schizoid personality" The situation at school deteriorates he becomes destructive and vents his feel ings on the furniture etc. At this point he also begins to show suspicion. In 1954 he stole money and behaved aggressively in school Appears to be depressed and suspicious. Social maladjustment increases during 1954 doing wilful damage breaking in an pilfering. In the classroom, he is on the move constantly crawling under the desks, etc. It is suggested that the boy should be sent to SkÅ, a therapy home for

social boys, but the parents are negative. However, he is placed in a therapy home in 1956. The staff at the Home consider him to be "a very peculiar boy" Despite this viewpoint, the parents request his return home and the request is granted the same year In 1957 he is admitted to Psychiatric Department for investigation and treatment. No change in circumstances. In 1960, he was admitted as an acute case to a Mental Hospital, and in 1963 to the Psychiatric Department of a general hospital where he was treated for the diagnosis of catatonic schizophrenia with sight, smell, taste and hearing hallucinations" and a catatonia approaching stupor"

Boy born 1939 Reported in 1952 on the grounds of bedwetting and finger-sucking. Mother has been inpatient at Mental Hospital Complete home, the eldest of two children. Closely knit family Normal pregnancy and partus. Retarded motoricity walked at 18 months, development otherwise unremarkable Physically healthy School performance and behaviour normal, reasonably good contact with schoolmates. Nothing of particular importance found upon examination. IQ 114 according to Terman-Merrill. Rorschach nothing psychotic. Counselling in general terms only Had grown out of his enuresis by 1953 Discharged from the CGC with the diagnosis Psychosomatic symptoms.

During the period 1959–63 the boy was hospitalized at a Psychiatric Department, the total time spent in hospital in excess of 4 years. Diagnosis Schizophrenia, demens. Invalidity pension

Affective psychoses

Girl born 1938 Reported in 1955 on the grounds of hyperactivity Previously depressed. No hereditary history Home circumstances unremarkable. Complete home Normal pregnancy Partus 6 weeks early in care of Children's Hospital for a short period Development normal but began refusing to eat at an early age. Uncommunicative and quiet but always well-behaved, clever at school. Has found it difficult to cope with schooling during the past 6 months, hyperactive, noisy disturbing and quarrelsome Upon examination, the girl was found to be depressed and trying to find help Self reproaching Her case interpreted as a state of acute depression, "possibly of an endogenic nature" Referred to a Psychiatric Department for hospitalization and is therefore discharged from the CGC with the diagnosis Psychosis.

At the Psychiatric Department she is given E.C.T but goes into a manic phase and is transferred to a Mental Hospital.

Hospitalized for a total of 5 months during 1955–1960 with the diagnosis Psychosis manica.

Girl born 1937 Reported in 1953 on the grounds of "pubertal problems" Mother previously hospitalized for psychiatric care Father went through a period of "brooding" Complete home The younger of two children. Pregnancy partus and development were all normal. Physically normal. Brother also physically normal. Mentally the patient was always "wilful" but happy and open, easy to make contact with very ambitious, clever and well-adjusted at school. For the past six months or so, she has been suffering from attacks of anxiety and self reproach. Upon examination, she was found to be depressed, unstable but satisfactory in her relationships. Feelings of inferiority and guilt—probably an endogenic depression. Rorschach depression. Medication, supportive contact. The picture changes after a few months. She becomes more fragmented, ambivalent, lacking initiative Both parents suffer depressions at this time and as the mother is admitted to hospital for psychiatric treatment the question arises of whether the girl should be boarded out. She is finally placed in a foster home, but things do not work out. She is irritable and quarrelsome. Placed in a Home for Girls. Starts a job but is fired after a quarrel with the boss "she talks too much" Returns to school but has to leave again, behaves in a "peculiar" manner tense and confused. Upon examination, she is found to be tense, exhalted, fluctuates between laughing and crying, disoriented. Opium medication. Referred to the child psychiatric department of the hospital where she is treated under the diagnosis of psychoneurosis (1953). Referred back to the

CGC afterwards. Receives supportive contact from the CGC in 1954 but becomes increasingly fragmented and loses her distance. Attempts a new job but soon leaves it. Oscillates somewhat, sometimes more contained. Re-admitted for psychiatric care in 1954 and considered to be in "a typical manic phase" within a manodepressive psychosis.

Discharged in 1955 with the diagnosis of psychosis. Has now been placed in a boarding school. Reported again in 1956 because she had disappeared from her home. She returned home after having spent large sums of money on male acquaintances. Re admitted for psychiatric care under the same diagnosis as above. Boarded out in family care after being discharged from the hospital.

Discharged from the CGC after being certified and admitted to a Mental Hospital in 1958. She been hospitalized for mental care for a total of 6 months during the years 1956–58. ...agnosis: Psychosis manica.

Girl born 1937. Reported in 1955 on the grounds of pilfering. Was forced to leave her job. No hereditary history. Complete home. The second of three siblings. Normal pregnancy, partus and development. Physically healthy. Always extrovert, active, "sloppy". Problems with friends who "got tired of her". No particular problems during her years at school. After leaving school, obtained employment but could not hold the job: careless, unconcentrated and pilfered. Upon examination she was found to be uncertain and tense, but easy to make contact with, rather gentle. Her condition is interpreted as an *emotional disturbance and supportive* contact is recommended. This contact is interrupted, however, as the patient has to be hospitalized for symptoms of apparent thyreotoxic character. She is discharged from the CGC with a diagnosis of behavioural disorder. Later she is admitted to the Mental Hospital for care on a number of occasions: 1957, 1958, 1960, 1962, 1963 and 1965, the diagnosis being manodepressive psychosis. Several of these admissions followed upon attempts at suicide. The total time spent in hospital was 1 year and 3 months.

Boy born 1945. Reported in 1949 on the grounds of aggressiveness. Reported again in 1954 because of restlessness at school and tics. Masturbates. Maternal uncle and paternal uncle are both psychotic. Complete family. Younger brother in good health. Pregnancy, partus and development unremarkable. Cried a lot as an infant. Would not eat from the age of 1 1/2 years. Always lively and aggressive, very attached to mother. Restless at school. Unconcentrated. Tics started at the age of 5 years, mobbed by peers. Upon examination, he was found to be immature for his age and unstable, but easy to make contact with. I.Q. 80 according to Terman-Merrill. Rorschach: "feeling of loneliness and isolation. Unclear grasp of reality." It is suggested that a thorough investigation be made of his case but his parents decline, and the case is therefore written off in 1954. He is reported again later the same year as he has begun pilfering at home. His school performance is the same as earlier: according to his teacher he is very childish. A neurological examination is suggested but refused. Recommendation of transfer to remedial class. The case is written off in 1955. Reported again in 1958, again for pilfering. Had coped reasonably well with remedial class schooling but the parents had "moralized". Is placed in a "winter colony" following recommendation to this effect but no other measures are taken. Discharged the same year. Diagnosis: mild environmental reactions.

Hospitalized at a Psychiatric Department in 1962, 1963 and 1964. Diagnosis: Mania.

Boy born 1944. Reported in 1951 because of *restless and disturbing* behaviour in school. Moping and complaining at home. Difficulties with friends. Hereditary history: maternal grandmother hospitalized for psychiatric treatment. Complete home, the oldest of 4 siblings. Pregnancy, partus and development unremarkable. Physically healthy. Started refusing to eat at the age of 2 years, still has to be fed occasionally. Difficulties in making contact with playmates, prefers younger children. Seems to be "tired and listless". Demands help with undressing. Restless at school, keeps to himself, passive

Upon examination, he shows bad posture and drags his feet, talks baby-talk" stammers. Seems to be immature for his age, unconcentrated, restless. IQ 112, according to Terman Merrill, blocked, split. Several more talks and examinations. While waiting for hospital investigation the boy is placed in an observation remedial class and spends time at a summer colony In 1952, his behaviour is calmer and he is somewhat more active Rorschach highly infantile picture. "The emotional adjustment to the environment is very poor" An attempt at group therapy is made but the patient refuses to attend after two meetings. Status quo in all respects. Monomanic interest in tram lines, knows all the routes and timetables. Very poor contact with friends. Increasingly mobbed during 1953 and reacts "hysterically The parents begin to "give upp" Starts playing truant during this year frequency of truancy increasing. In 1955 he is taken in charge by the social welfare authorities and placed in a foster home

Discharged from the CGC in 1955 Diagnosis behavioural disorder

Hospitalized for psychiatric care in 1963 and 1966, with a diagnosis of a manodepressive condition.

Boy born 1940 Reported in 1946 and in 1955 on the grounds of fear insecurity and anxiety The father and the paternal grandmother are diagnosed as manodepressive psychotics. Complete family twin sister normal. Normal home circumstances. Normal pregnancy and partus. Development unremarkable. Physically healthy An easily handled and "good" child but sensitive when he was small. Dependent on mother When he was 5 years old and living with his maternal grandparents (father ill), he began to show anxiety sometimes feelings of panic. This lasted about 6 months. At about the age of 11 or 12, he manifested paranoidal and hypochondriacal ideas became unconcentrated, performed unsatisfactorily at school. This lasted for several years. For the past 6 months or so, he has been suffering from anxiety he is afraid of becoming ill, afraid of being poisoned. Agoraphobia. Follow rituals. Admitted to Child Psychiatric Department for investigation and is given diagnosis Psychosis manico-depressiva + React c phobica. He is considered to be depressed—good intelligence level—paranoidal delusions and obsessions. During a period he was hypomanic acting with increasingly indiscriminate actions. When he established personal contact with the hospital, he is discharged from the CGC (1955) with a diagnosis of psychosis. His case is opened again on three occasions in 1955–56 when he is hospitalized for diagnosed manic-depressive psychosis Anxiety neurosis. Hospitalization for a total time of 11 months.

Reactive psychoses

Girl born 1938 First reported in 1945 subsequently in 1948 and 1953 initially because she was too immature to start school No hereditary history Complete family The second of two children. The sister is in good health. Pregnancy and partus normal. Generalized late development. Mentally a happy and well-adjusted child When examined in 1945 was found to be generally immature for her age. IQ 82, according to Terman-Merrill. Delay of school start recommended Status quo the following year Recommendation of normal class. The 1948 report is made because she cannot cope with school, is uncertain and inhibited The mother cannot understand the child's difficulties. Remedial class recommended. Case closed Case re-opened in 1953 because the girl withdraws from contact with other children, is the victim of mobbing. Completely isolated from schoolmates. She is discharged from the CGC as she refused to maintain contact. The diagnosis given was Delayed development, mild environmental reactions. In 1963 the patient was hospitalized at the Psychiatric Department for a diagnosis of Psychosis puerperarum.

Girl, born 1933 Reported in 1941 new report in 1953 Initial grounds were problems at school. No hereditary history Complete home good circumstances. Only child. Normal pregnancy and partus. Generalized late development, especially in speaking. A good, pleasant child immature in general. Could not manage ...

Supplement 5 Length of treatment in inpatient psychiatric care

	Age at discharge (years)							
	0–6.5		6.6–11.5		11.6–15.5		15.6–	
	M 304	F 222	M 656	F 289	M 384	F 150	M 133	F 130
Child psychiatric inpatients dept								
Less than 1 month	22	3	22	5	9	1	—	—
1–6 months	7	2	15	4	4	2	—	1
7–12 months	—	—	1	—	1	1	—	—
13–24 months	—	—	—	—	—	—	—	—
More than 24 months	—	—	—	1	—	—	—	—
Adult psychiatric inpatients dept								
Less than 1 month	—	—	4	1	7	7	3	4
1–6 months	1	—	7	1	13	5	7	14
7 12 months	—	—	1		12	1	1	1
13–24 months	—	—	3	—	2	1	—	2
More than 24 months	—	—	1	—	2	—	2	4
Total, child + adult psychiatric inpatients								
Less than 1 month	22	3	23	5	13	5	3	4
1–6 months	8	2	20	4	17	8	7	15
2 months	—	—	2	1	2	1	1	1
4 months	—	—	3	1	2	—	—	2
4 months	—	—	1	1	2	1	2	4

Supplement 6 Diagnoses confirmed during psychiatric care during the observation period

	Age at discharge									
	0–6.5		6.6–11.5		11.6–15.5		15.6–		Total	Total
Diagnoses	M 304	F 222	M 656	F 289	M 384	F 150	M 133	F 130	M 1 477	F 791
Total psychoses	3	1	6	1	5	4	1	9	15	15
Child psych. diagnosis	3	1	—	—	2				5	1
Adult psych. diagnosis	—	—	4	—	3	4	1	7	8	11
Child + adult diagnosis	—	—	2	1	—					3
Total neuroses	26	15	71	25	45	22	12	29	154	91
Child psych. diagnosis	25	14	64	20	25	5	2	3	116	43
Adult psych. diagnosis	—	1	5	4	16	14	10	25	31	44
Child + adult diagnosis	1	—	2	1	4	3	—	1	7	5
Total character disorders	6	—	20	4	20	4	8	7	54	13
Child psych. diagnosis	6	—	10	1	5	2	—	—	1	1
Adult psych. diagnosis	—	—	10	3	12	2	8	7	30	12
Child + adult diagnosis	—	—	—	—	3	—	—	—	3	
Total behavioural disorders and environmental reactions	54	26	115	54	50	21	10	16	229	117
Child psych. diagnosis	54	25	110	52	45	20	8	9	217	106
Adult psych. diagnosis	—	1	1	1	4	—	2	6	7	8
Child + adult diagnosis	—	—	4	1	1	1	—	1	5	1
Total developmental disorders	31	11	21	22	2	1	2	8	56	42
Child psych. diagnosis	30	11	21	19	2	—	—	5	51	[illegible]
Adult psych. diagnosis	1	—	—	2	—	1	2		3	[illegible]
Child + adult diagnosis	—	—	—	1	—	—	—	1	—	[illegible]
Total epilepsy, brain damage	8	2	14	3	5	—	3		30	7
Child psych. diagnosis	8	2	13	2	4	—	—	—	25	4
Adult psych. diagnosis	—	—	1	—	1	—	3	2	5	2
Child + adult diagnosis	—	—	—	1	—	—	—	—	—	1
Total healthy, social problems, word-blindness	—	1	10	3	2	2	—	3	12	9
Child psych. diagnosis	—	1	10	2	1	—	—	—	11	1
Adult psych. diagnosis	—	—	—	1	—	2	—	3		6
Child + adult diagnosis	—	—	—	—	1	—	—	—	1	

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Chronic Nonspecific Respiratory Disease in Children, a Five Year Follow-up Study

By K.F. KERREBIJN H.C.A. HOOGEVEEN SCHROOT and M.C. VAN DER WAL

ALMQVIST & WIKSELL PERIODICAL COMPANY STOCKHOLM SWEDEN

Chronic Nonspecific
Respiratory Disease in Children
a Five Year Follow up Study

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CONTENTS

1 INTRODUCTION

Asthma, chronic bronchitis and emphysema (chronic nonspecific respiratory disease, CNSRD) are common conditions in adults (32, 34) and children (29) in the Netherlands. Many children with symptoms belonging to the CNSRD syndrome will continue to have these into adult life[1] (3 9 17 21 23 42, 44 53 54). The various studies concerning the history of CNSRD in childhood are hardly comparable as regards their design and results. The definitions of asthma, asthmatic bronchitis, recurrent bronchitis and chronic bronchitis in children and the criteria for recovery or improvement are not sufficiently clear Recent and previous symptoms are often not differentiated. The critical evaluation of the effect of treatment on the course of the disease is insufficient in most studies.

In the majority of children, the symptoms of CNSRD begin in the first five years of life. The chance that they will persist into adulthood seems to be least in those children, in whom symptoms are not frequent or slight and disappear during school age Some findings suggest that optimum treatment and favourable psychosocial conditions have a beneficial effect on the course of the disease. However to quantitate these is difficult.

It will therefore often be impossible to make a reasonable prediction of the prognosis of CNSRD in childhood for adult life. In order to ensure optimum curative and preventive medical care, it will be essential to examine the conditions in which the injurious effects of exogenous factors, such as allergens, infections, chemical and physical agents and unfavourable psychosocial circumstances, ar reduced to a minimum. However studies on the relative significance of various exogenous factors are difficult to perform. These studies are merely practicable in homogeneous, clearly defined populations living under specific conditions in which only a limited number of exogenous factors play a role.

In view of the morbidity of CNSRD the most extensive possible preventive care in addition to optimum treatment of signs and symptoms is essential. Among others, this will include counselling of smokers, vocational guidance advice on housing, etc. This is of importance in adults and, to an even greater extent, in subjects in the 10–20 year range, in whom adequate health care and health counselling will contribute to a favourable course

In adults morbidity and absenteeism due to CNSRD would presumably be considerably reduced if children running and increased risk of CNSRD in later life could be selected at an early stage and given adequate care.

This aspect, i.e. the selection of children running an increased risk, is the subject of the present study

2. EPIDEMIOLOGY OF CNSRD

2.1 PREVALENCE

For the literature on the prevalence of CNSRD in the Netherlands and other countries, the reader is referred to the thesis by Van der Lende (31) and a number of papers published by the TNO Working group on the Epidemiology of CNSRD (33 34).

[1] A detailed review of this literature is available at the author

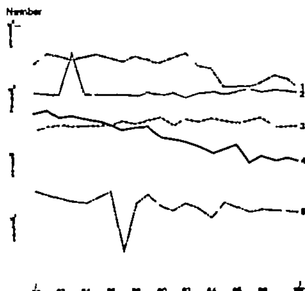


Fig 1 Deaths by congenital malformations (1) (numbers 750–759 (–'68), 740–759 ('69+)), accidents (2) (numbers E800–E999), neoplasms (3) (numbers 140–239), pneumonia (4) (numbers 490–493 (–'68), 480–486 ('69+1)), and chronic non specific lung diseases (5) (numbers 241 502, 526, 527 1 (– 68), 493 391 518, 492 ('69+), boys and girls, 0-14 years of age, 1950-1971 The Netherlands. Numbers of the international statistical classification of diseases, injuries and causes of death.

2.2. ABSENTEEISM DUE TO SICKNESS

Table 1 shows absenteeism due to a number of chronic and acute conditions in the Netherlands in 1958, 1963 and 1966 More recent data have not been published

Among the chronic conditions, chronic respiratory disease (mainly CNSRD) is the next important cause of absenteeism after cardiovascular disease Absenteeism was estimated at from 10 000 to 11 000 man years in 1966

The considerable social significance of acute respiratory conditions which cause five times the absenteeism due to chronic respiratory disease is accentuated by the table. It should be pointed out that it is not impossible but even likely that part of the absenteeism resulting from acute respiratory conditions occurs in cases of chronic respiratory disease and is directly due to the latter The figures reported for chronic respiratory disease as the cause of absenteeism are therefore likely to be minimum figures.

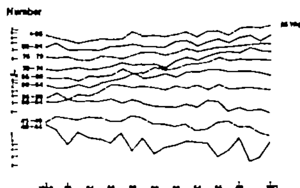


Fig 2 Mortality from chronic nonspecific lung diseases (numbers 241 502, 526, 527 1) (–'68), 493 491 518, 492 ('69+)), males, per 100 000 of each age group, 1950–1971 The Netherlands. Numbers of the international statistical classification of diseases, injuries and causes of death.

2.3 MORTALITY

In 1968 Speizer (47) and his associates published mortality rates from asthma in a number of countries. These showed a marked increase in subjects in the 10–19 year range in Great Britain Japan and Australia. It was suggested that this could have been due to the excessive use of aerosol bronchodilators and the fact that administration of steroids during exacerbations was inadequate.

Table 2 shows the death rates from asthma and chronic bronchitis in subjects in the 0-39 year range per 100 000 of each age group in the Netherlands. The rates are very low and there was no increase during the period from 1959 to 1971

The difference in mortality rates between the

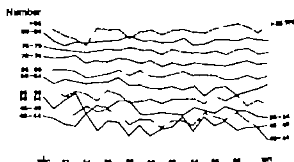


Fig 3 Mortality from chronic nonspecific lung diseases (numbers 241 502, 526, 527 1 (–'68), 493, 491 518, 492 ('69+)), females, per 100 000 of each age group, 1950-1971 The Netherlands. International statistical classification of diseases, injuries and causes of death.



Fig 4 Deaths by chronic bronchitis and emphysema, — (numbers 502+527 1 (– 68) 491+492 ('69→)) and asthma, – – (numbers 241 (–'68), 493 ('69→)), males, 55–59 years of age, 1950–1971 The Netherlands. Numbers of the international statistical classification of diseases, injuries and causes of death.

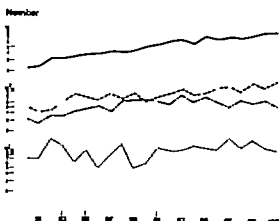


Fig 5 Mortality from chronic bronchitis and emphysema (numbers 502 resp. 527 1 (–'68), 491 resp. 492 ('69→)) compared to mortality from arteriosclerotic heart disease (numbers 420 (–'68), 410, 411 412, 413 414 ('69→)), men (— —) and women (– – —), 50–54 years of age, The Netherlands. Numbers of the international statistical classification of diseases, injuries and causes of death.

Netherlands and Great Britain is hard to account for particularly as the clinical picture and general schedules of treatment are comparable in the two countries.

In Figure 1 the number of subjects in the 0–14 year range who died from CNSRD is compared with the number of deaths from congenital malformations, accidents, neoplasms and pneumonia. These figures also show that CNSRD is a minor cause of death in children.

Figures 2 and 3 show the mortality from CNSRD per 100 000 men and women over forty Mortality is higher in men than it is in women. The men show an increase from the 55th year of life This begins about the year 1954 The increase is caused by chronic bronchitis and emphysema, as is apparent from Figure 4 (This figure is concerned with subjects in the 55–59 year range it also holds true, however for the older age groups.) The cause of this increase is obscure. Increased cigarette smoking may possibly be a factor An outstanding feature is the fact that the mortality from bronchitis and emphysema runs parallel to that from cardiovascular disease although absolute mortality is lower This is illustrated in Figure 5 for those in the 50–54 year range.

3 STUDY DESIGN AND OBJECTIVES

From 1968–1972 a follow-up study on symptoms and signs of CNSRD was performed in randomly selected populations of schoolchildren in Rotterdam.

The aim was to investigate the appearance or disappearance of symptoms of CNSRD and to select children running an increased risk of CNSRD in adult life by means of a standardized questionnaire. This was supplemented by pulmonary function tests, determination of the bronchial reactivity allergy skin tests, chest radiography and investigations about social factors, air pollution, parental smoking habits and parental respiratory symptoms.

4 POPULATIONS STUDIED

4 1 In 1968 this consisted of

(1) 175 boys and 175 girls born during the period from October 1960 to October 1961 and living in the Hoogvliet district.

(2) 175 boys and 175 girls born during the period from October 1955 to October 1956 and living in the Hoogvliet district

(3) 175 boys and 175 girls born during the period from October 1960 to October 1961 and living in the IJsselmonde district

(4) 175 boys and 175 girls born during the period from October 1955 to October 1956 and living in the IJsselmonde district.

The total number was 700 children of Hoogvliet and 700 children of IJsselmonde *This population will henceforth be referred to as population A* These were randomly selected populations taken from children born during the above periods and living in Hoogvliet and IJsselmonde on October 1 1967 They were chosen for the following reasons

(1) Clinical experience has shown that changes in the occurrence of symptoms of CNSRD can be expected in the 6–16 year range.

(2) The two districts are newly constructed areas with favourable housing and social conditions.

(3) Industrial air pollution was greater in the Hoogvliet district than it was in the IJssel monde district at the beginning of the study

4.2. As it was advisable to increase the number of children with symptoms in view of the follow up 255 children of the relevant cohorts, who were recorded as having symptoms of CNSRD by the school medical officers and living in Hoogvliet and IJsselmonde were selected in 1969 The findings in these children were used only in longitudinal studies and not in data on prevalence *This population will be further referred to as population B*

4.3 The numbers and proportions of children of populations A and B who fully took part in the study during the period from 1968 to 1972 are listed in Table 3 In each year the children are equally distributed over the districts and sexes the number of those of the older cohort taking part is slightly smaller than is that of those of the younger cohort. (The difference was approximately 10 per cent in 1972.) The reasons for not taking part were traced wherever possible by home visits or telephone calls. Although specific inquiries were made in this regard, respiratory symptoms were not stated as the reason in any of these cases. Change of residence was the reason in approximately one-third of those who did not take part in the study during the period from 1969 to 1972 the other most often stated reasons were

— objections to committing oneself to a five-year period
— objections on schoolabsence
— objections on principle
— inadequate interest in the study
— family reasons
— severe mental or physical disorders in the child to be studied
— refusal on the part of the child.

5 METHODS OF INVESTIGATION

5 1 QUESTIONNAIRES ON SYMPTOMS

5 1 1 *General*

A European Coal and Steel Community (ECSC) questionnaire modified for children was used in taking the medical histories of the children In 1968 the histories concerned the last two years in the next few years, they only concerned the year just ended. The questions were asked by two investigators (physicians) In 1968,

the parents were sent a questionnaire in advance with the request to complete it at home. The questions asked in the questionnaire were broadly similar to those asked during the investigation. This self-administered questionnaire was designed to prepare the parents for the questions that would be asked during the investigation. It was regarded as essential that the answers should reflect reality wherever possible, i.e., that the methods adopted in this study should discriminate as sharply as possible. For this reason, the original ECSC questionnaire was modified to some extent as early as 1968 Specifically the following passage was included orally in questions 1-3 after "usually" "that is to say as many as five days a week on average" Moreover questions 4 and 5 were added, in which it was explicitly stated what was meant by "three months a year" namely three *consecutive* months a year Table 4 shows that this makes a considerable difference in the number of affirmative answers. The questionnaire was extended with questions on cough for two months and one month in 1969 Therefore the numbering of the questions had to be changed in 1969 It is already indicated in the text and the tables to which year the numbering of a question refers The questionnaire is given in Appendix I.

5.1.2. *Reliability of the questionnaire*

(1) The answers to question 36 *k* (1968) ("Did your child ever have any attacks of bronchitis or asthma?") were compared with those to questions on cough, dyspnoea and asthmatic attacks. All children examined were classified into one of four symptom groups (dyspnoea + cough + (D + C +) dyspnoea + cough − (D + C −) dyspnoea − cough + (D − C +) dyspnoea − cough − (D − C −). For details, see Section 6.1 p. 15).

This comparison did not justify any doubt as to the correctness of the answers to the questions used in classifying the children into symptom groups.

(2) It was checked whether children showing symptoms of CNSRD which were severe enough for referral to the outpatient department of the respiratory unit of the Sophia Children's Hospital, always were classified into one of the symptom-positive groups after their parents had answered the questionnaire. This was done in 76 children. Independently another investigator attempted to answer the questionnaire using the children's hospital records.

The difference between and similarity of the answers to each question in the records and questionnaire have been recorded.

Fifty-nine percent of the answers were identical in the records and questionnaire whereas this was not the case with twenty-seven percent. Fourteen percent of the answers were not reliable.

The similarity was found to be most marked in questions relating to the previous histories of the subjects. In view of the background of the children, this is an obvious finding.

Cough was less frequently coded in the affirmative according to the questionnaire than it was according to the records. The similarity of the questions on dyspnoea was fairly close.

Conclusion In the children showing respiratory symptoms, there is inadequate similarity between the findings in the questionnaire and those in the records as regards the symptom cough and fairly adequate similarity where the symptom dyspnoea is concerned. The questionnaire shows an underreporting of the symptom cough.

(3) A number of the variables included in the study such as cough and dysponoea, are marked by dichotomy of the values, i.e., they show whether a particular symptom has or has not occurred or whether it is present.

Efforts were made to study the variations in frequency distribution of such a variable from one survey to another The following parameters were introduced for this purpose

p = possibility in errors of coding
P = possibility of appearance of the symptom with which the question is concerned at the time of the first survey

τ = possibility of the symptom having occurred during the interval between the first and second surveys.

The values of p P and τ about the variables "history of eczema" (question 47*a* (1969)) and "tonsils removed" (question 36*e* (1968)) have been estimated by the maximum likelihood method. This was done separately in four groups. These groups differed from one another in that they were questioned by different inter viewers in at least one of the two years during which inquiries were conducted These questions are best suited to verify the reproducibility of the result obtained, as a finding which was positive in 1968 should continue to be so during the following years. The calculated estimates of the values of p P and τ are shown in Tables 5 and 6 The groups in these tables are com posed according to the numbers of the successive interviewers group 1–3 for instance includes those children who were interviewed by interviewer 1 in 1968 and interviewer 3 in 1969 [1]

The tables show that the estimated value of τ (the percentage of faulty codings) continues be very low It is highest in group 2–3

(4) In fifty children of the oldest birth cohort, the questionnaires were separately submitted to the mother and the child at several weeks intervals. The similarity between the answers given on the two occasions ranged from good to excellent.

(5) As is apparent from Tables 12 and 13 the mean one-second forced expiratory volume ($FEV_{1.0}$) and the mean forced expiratory volume expressed as a percentage of the vital capacity (FEV) of children with dyspnoea on exer tion are significantly lower than those in children showing no respiratory symptoms (D – C – c – w – n –) (for further explanation of these tables, see p. 18)

Conclusion drawn from studies on the reliability of the questionnaire The answers to the questions asked in the questionnaire appear to be fairly reliable and readily reproducible Appreciable differences between interviewers were not observed. Comparison of the results obtained using the questionnaire with the findings in the records of the out patient department is not possible. A small proportion of the out patients to whom the questions of the questionnaire were put were classified with the group in which symptoms were absent. This was probably due to the fact that treatment had reduced the symptoms to such an extent in these cases that they no longer satisfied the criteria adopted for the groups in which symptoms were present. This may naturally also be the case in population surveys and may result in an unduly low symptom prevalence rate. The symptom most difficult to evaluate is dyspnoea on exertion. The $FEV_{1.0}$% of children who showed only this symptom is significantly lower than that in nondyspnoeic subjects, which supports the reliability of the indicative value of this question. Appendix II includes a review of the literature on observer s errors.

5.2. SOCIAL QUESTIONNAIRE

In 1969 and 1970 the homes of all children who had taken part in the entire survey in 1969 were visited A questionnaire on social and demographic data was completed by a health visitor trained for this work. If required, she explained the purpose of the survey in greater detail and also urged people to continue taking part in it to the best of their ability This data was collected for the purpose of obtaining information on the social and demographic back grounds of the children under investigation and their families.

5.3 QUESTIONNAIRE ON THE STATE OF HEALTH OF PARENTS, BROTHERS AND SISTERS

In 1972, the parents were sent a questionnaire for the purpose of collecting data on the family background of respiratory symptoms and smok ing habits (36)

[1] In 1969 interviewer 3 took the place of interviewer who had to discontinue her activities because of change of residence.

5.4 PHYSICAL EXAMINATION

The upper and lower respiratory tract were physically examined each year. In addition, the height, weight and physical development were measured by standardized methods (39, 48).

5.5 FUNCTION TESTS

Pulmonary function tests were performed and the histamine threshold was determined each year. This was done in population A from 1968 in the oldest and from 1969 in the youngest cohort and in population B from 1969. Pulmonary function tests were invariably performed between the end of April and mid-June to avoid accidental diminution because of respiratory symptoms due to seasonal factors as much as possible. They were only performed when no respiratory symptoms were present at the time of investigation.

5.5.1 *Pulmonary function tests*

The following values were determined:

(1) In all children the vital capacity (VC) and one second forced expiratory volume ($FEV_{1.0}$) using a Lode water sealed spirometer (model D 53).

(2) In a limited number of randomly selected children of each birth cohort, the total lung capacity and the residual volume by means of the He method, using a volumograph no. 4 (Mijnhardt).

5.5.2. *Histamine threshold*

The reactivity of the bronchi was determined by the histamine threshold (52) using the expiratory peak flow instead of the VC and FEV as parameters of bronchial obstruction. The expiratory peak flow was measured with a Wright peak-flow meter.

5.5.2.1 *Comparison of the histamine threshold as measured with the spirometer and with the Wright peak-flow meter.* In 327 children (those taking part in the population survey as well as children attending the out-patient department of the respiratory unit of the Sophia Children's Hospital), the histamine threshold was determined by the spirometer and by the Wright peak-flow meter. The results of the two methods of determination were in good agreement.

5.5.2.2. *Reproducibility of the histamine threshold.* In Table 7 the number of children of population A in whom various determinations of the histamine threshold were carried out during the period from 1968 to 1970 are listed. Normal or slightly lowered histamine thresholds (16 – >32 mg/ml) are readily reproducible; markedly lowered thresholds (<8 mg/ml) often show an improvement.

5.5.2.3 *Relationship between initial pulmonary function and histamine thresholds.* This was studied in a separate survey (Appendix III). This study showed that there is some relationship between the initial FEV_1 or the peak flow and the histamine threshold. When the histamine threshold is known, however, it is not possible to even approximately predict the $FEV_{1.0}$, nor can the histamine threshold be predicted when the $FEV_{1.0}$ is given. Repeated measurements of pulmonary function and the histamine threshold showed that these often show an opposite trend (i.e. histamine threshold decreases and pulmonary function increases or vice versa).

Conclusion. The determination of the histamine threshold as a parameter of the bronchial reactivity seems to be useful in addition to the measurement of the pulmonary function. These two quantities are probably largely determined by different factors. The histamine threshold is readily reproducible in the normal and slightly lowered range when it is measured over a number of years. It would be of major importance to know whether a histamine threshold which is permanently lowered (i.e., also during an optimum clinical period in which the VC and FEV are within normal limits) has any significance for the prognosis.

5.6. ALLERGY TESTS

Tests for cutaneous allergy to house dust, mixed moulds, grass pollen[2] and danders[3] were

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[1] *The mixed moulds included:* Trichoderma viride, Fusarium culmorum, Cladosporium, Cladosporiodes, Cladosporium elatum, Cladosporium herbarum, Rhizo-

performed in population A in 1968 and in population B in 1969 Testing with house dust, grass pollen and danders could be repeated in a number of children in the spring of 1973 after the main study had been completed, by the same technicians.

The allergens used were Diephuis allergens at the following concentrations intracutaneous injection of 0 5 mg/ml of house dust and, in the case of a positive reaction, additional injection of 0 05 mg/ml and 0.005 mg/ml intra cutaneous injection of 0.2 mg/ml of mixed moulds and when a positive response was obtained, additional injection of 0 02 mg/ml and 0 002 mg/ml, intracutaneous injections of 1 000 Noon units of grass pollen and, for positive reactors, additional injection of 100 Noon units and 10 Noon units intracutaneous injection of 0.25 mg/ml of danders and, in the event of a positive response additional injection of 0 025 mg/ml and 0.0025 mg/ml.

The allergens used in 1973 were of the same ... as those used during previous years. They ... been stored in the freeze-dried state

...pus nigricans, Stemphylium botryosum, Alternaria tenuis, Penicillium brevi compactum, P expansum, P notatum, P frequentans, P commune, Aspergillus versicolor Aspergillus niger Aspergillus fumigatus, Mucor spinosus, Mucor mucedo, Mucor racemosus, Pullularia pullulans, Botrytis cenerea, Merculius domesticus, Epicoccum purpurascens.

The grass pollen included: Secale cereale (rye), Dactylis glomerata (cocksfoot grass), Lolium perenne (rye-grass), Anthoxantum odoratum (sweet vernal grass), Alopecurus pratensis (meadow foxtail grass), Agrostis alba (white bent), Holcus lanatus (Yorkshire fog), Cynosurus cristatus (crested dogtail).

Human and animal danders. Man, horse, swine, cat, goat, cattle, rabbit,dog, sheep and various birds.

To study the repeatability of the tests for cutaneous allergy in individuals showing a positive response skin testing was repeated in a number of asthmatic patients of the Sophia Children s Hospital with positive intracutaneous reactions. These patients were treated but had not been desensitized. The technicians per forming the skin tests were not aware of the results of the previous tests. The repeatability was, on the whole, highly satisfactory in those age groups in which the present study was carried out

5 7 RADIOGRAPHY

5 7 1 *Radiography of the lungs*

In 1968, X rays of the lungs were made in all children of population A and, in 1969 in all those who were studied in population B These X rays were read by H. A van Geuns, M D without knowing the children or their medical histories. He used a standardized method in which particular attention was paid to the lung pattern and hili.

5 7.2. *Determination of bone age*

X rays of the left hand of all children were taken each year to determine the bone age in order to correlate this with height growth, development of puberty and pulmonary function. In each case the bone age was determined by the same investigator (H.H −S) using Tanner's method (49).

6. RESULTS

6 1 CLASSIFICATION INTO SYMPTOM GROUPS

For a convenient arrangement of the results, the following classification into symptom groups was made It was based on the *major symptoms* of CNSRD i.e. prolonged cough, dyspnoea on exertion and attacks of asthma (Text table 1).

A classification into four symptom groups was based on the scheme D+C+ D+C− D−C+ and D−C−

In the rating dyspnoea + questions 15 and 24 of 1968 and questions 15 18 27 and 29 of

Text-table 1 *Classification into symptom groups based on major symptoms*

Dyspnoea	Questions 24 (1968), 27 and,or 29 (1969)· When resting did your child ever have attacks of shortness of breath with wheezing at rest (asthmatic attacks)?	Questions 15 (1968), 15 and/or 18 (1969)· Has your child ever been troubled by shortness of breath when playing outdoors or walking up a staircase
D+	Yes	Yes
	Yes	No
	No	Yes
D−	No	No
Cough	Question 4 (1968) Question 6 (1969) Did your child cough like this* on most days in winter for as much as three or more consecutive months?	Question 5 (1968) Question 9 (1969) Did your child cough like this* on most days in summer for as much as three or more consecutive months?
C+	Yes	Yes
	Yes	No
	N	Yes
C−	No	No

i.e. continuously that is on average 5 days a week.

1969 were combined, as it is difficult to adequately differentiate between dyspnoea on exertion and dyspnoea at rest in children.

The D–C group was subdivided into on the basis of "secondary" symptoms (Text table 2)

6.2. PREVALENCE OF COUGH, DYSPNOEA ON EXERTION ASTHMATIC ATTACKS AND RHINITIS IN POPULATION A

Table 8 includes a summary for each year of investigation, based on the birth cohort and sex per symptom group In Table 9*a* the number and percentage of children according to the year of investigation and the age of the children are listed for each symptom and birth cohort.

In Table 9*b*, this was done for the combination of symptom-positive groups (D+C+ D+C− D−C+) per birth cohort and sex. The percentages listed in Tables 9*a* and 9*b* are summarized in Table 9*c* having been arranged by age. The number and percentage of children in whom a particular symptom was present for 0, 1 2, etc., years are stated in Table 10*a*. The number and percentage of children classified in one of the symptom-positive groups for 0, 1 2, etc., years are shown in Table 10*b*

The following can be deduced from these tables

(*a*) The total number of children taking part for five years consisted of 428 of the youngest group (61 1 percent of the initial number) and 389 of the oldest group (55.6 percent). As is

Text-table 2. *Subdivision of D–C-groups*

Cough	Wheezing	Nasal catarrh	Codes in tables
+	+		c+w+
+	−	−	+w− −
+	−	−	+w+ −
+	−	+	c+w− +
−	+	−	c−w+ −
−	−	+	c−w− +
−	+	+	−w+n+
−	−	−	−w−n−

c(ough) = affirmative answer to questions 1 and/or 2 and/or 3 (1968); questions 1 and/or 2 and/or 3, and/or 4 and or 5 (1969).
w(heezing) = affirmative answer to question 19 (1968)· questions 23 and,or 25 (1969).
n(asal catarrh) = affirmative answer to questions 29 and/or 30 (1968)· 34 and/or 35–37 and or 38, and or 39–41 (1969).

performed in population A in 1968 and in population B in 1969. Testing with house dust, grass pollen and danders could be repeated in a number of children in the spring of 1973 after the main study had been completed, by the same technicians.

The allergens used were Diephuis allergens in the following concentrations: intracutaneous injection of 0.5 mg/ml of house dust and, in the case of a positive reaction, additional injections of 0.05 mg/ml and 0.005 mg/ml; intracutaneous injection of 0.2 mg/ml of mixed moulds and when a positive response was obtained, additional injection of 0.02 mg/ml and 0.002 mg/ml; intracutaneous injections of 1 000 Noon units of grass pollen and, for positive reactions, additional injection of 100 Noon units and 10 Noon units; intracutaneous injection of 0.25 mg/ml of danders and, in the event of a positive response, additional injection of 0.025 mg/ml and 0.0025 mg/ml.

The allergens used in 1973 were of the same batch as those used during previous years. They [illegible] been stored in the freeze dried state.

[illegible] Stemphylium botryosum, Alternaria tenuis, Penicillium brevi-compactum, P. expansum, P. notatum, P. frequentans, P. commune, Aspergillus versicolor, Aspergillus niger, Aspergillus fumigatus, Mucor spinosus, Mucor mucedo, Mucor racemosus, Pullularia pullulans, Botrytis cinerea, Merulius domesticus, Sporotrichum purpurascens.

The grass pollen included: Secale cereale (rye), Dactylis glomerata (cocksfoot grass), Lolium perenne (rye-grass), Anthoxanthum odoratum (sweet vernal grass), Alopecurus pratensis (meadow foxtail grass), Agrostis alba (white bent), Holcus lanatus (Yorkshire fog), Cynosurus cristatus (crested dogstail).

Human and animal danders: Man, horse, swine, cat, goat, cattle, rabbit, dog, sheep and various birds.

To study the repeatability of the tests for cutaneous allergy in individuals showing a positive response, skin testing was repeated in a number of asthmatic patients of the Sophia Children's Hospital with positive intracutaneous reactions. These patients were treated but had not been desensitized. The technicians performing the skin tests were not aware of the results of the previous tests. The repeatability was, on the whole, highly satisfactory in those age groups in which the present study was carried out.

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5.7.1. *Radiography of the lungs*

In 1968, X-rays of the lungs were made in all children of population A and, in 1969, in all those who were studied in population B. These X-rays were read by H. A. van Geuns, M.D. without knowing the children or their medical histories. He used a standardized method in which particular attention was paid to the lung pattern and hili.

5.7.2. *Determination of bone age*

X-rays of the left hand of all children were taken each year to determine the bone age in order to correlate this with height growth, development of puberty and pulmonary function. In each case, the bone age was determined by the same investigator (H.H.-S) using Tanner's method (49).

6. RESULTS

[illegible]

[illegible]

[illegible] attacks of asthma (Text-table 7).

A classification into four symptom groups was based on the scheme: D−C−, D−C+, D+C− and D+C+.

[illegible] the rating dyspnoea — questions 1, [illegible] of 1968 and questions 15, 18, 27 and 29 of

[illegible]

Text-table 1 *Classification into symptom groups based on major symptoms*

Dyspnoea	Questions 24 (1968), 27 and or 29 (1969) When resting did your child ever have attacks of shortness of breath with wheezing at rest (asthmatic attacks)?	Questions 15 (1968), 15 and or 18 (1969). Has your child ever been troubled by shortness of breath when playing outdoors or walking up staircase.
D+	Yes Yes No	Yes No Yes
D−	No	No
Cough	Question 4 (1968) Question 6 (1969) Did your child cough like this* on most days in winter for as much as three or more consecutive months?	Question 5 (1968) Question 9 (1969) Did your child cough like this* on most days in summer for as much as three or more consecutive months?
C+	Yes Yes No	Yes No Yes
C−	No	No

* i.e. continuously that is on average 5 days a week.

1969 were combined as it is difficult to adequately differentiate between dyspnoea on exertion and dyspnoea at rest in children.

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+	−	+	c+w− +
−	+	−	−w+n−
−	−	+	−w− +
−	+	+	c−w− +
−	−	−	c−w− −

c(ough) −affirmative answer to questions 1 and/or 2 and or 3 (1968)· questions 1 and/or 2 and/or 3 and/or 4 and/or 5 (1969).
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The allergens used in 1973 were of the same batch as those used during previous years. They had been stored in the freeze-dried state

pos nigricans, Stemphyllium botryosum, Alternaria tenuis, Penicillium brevi compactum, P expansum, P notatum, P frequentans, P commune, Aspergillus versicolor Aspergillus niger Aspergillus fumigatus, Mucor spinosus, Mucor mucedo, Mucor racemosus, Pullularia pullulans, Botrytis cenerea, Merculius domesticus, Epicoccum purparascens.

The grass pollen included: Secale cereale (rye), Dactylis glomerata (cocksfoot grass), Lolium perenne (rye-grass), Anthoxantum odoratum (sweet vernal grass), Alopecurus pratensis (meadow foxtail grass), Agrostis alba (white bent), Holcus lanatus (Yorkshire fog), Cynosurus cristatus (crested dogtail).

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6 RESULTS

6 1 CLASSIFICATION INTO SYMPTOM GROUPS

For convenient arrangement of the results, the following classification into symptom groups was made It was based on the *major symptoms* of CNSRD i.e. prolonged cough, dyspnoea on exertion and attacks of asthma (Text-table 1).

A classification into four symptom groups was based on the scheme D+C+ D+C− D−C+ and D−C−

In the rating dyspnoea + questions 15 and 24 of 1968 and questions 15 18, 27 and 29 of

several years, followed by "three consecutive months a year" Coughing for two consecutive months or for one month is only occasionally listed more than once Among the respiratory symptoms listed in this table, dyspnoea on exertion is most frequently described as having been present for several years.

As was previously apparent from Tables 9*a* and 9*c*, Table 10*a* shows that the prevalence of cough is much lower in the oldest birth cohort than it is in the youngest. This also holds true for attacks of asthma and rhinitis but not for dyspnoea on exertion.

As is shown by Table 10*b* approximately 2 percent of the children of the two birth cohorts belonged to one of the symptompositive groups for five consecutive years. This was the case with from 2 to 4 percent for four or three years.

Conclusions

(1) In most children showing symptoms of prolonged cough, dyspnoea or attacks of asthma, symptom shifts take place over the years. These are not reflected in the transversal prevalence rates.

(2) The symptom-positive groups—the prevalence of which does not vary markedly in the two birth cohorts during the various years of investigation—partly include a varying population. This means that a population of schoolchildren characterized as "positive for CNSRD" in a transversal study may include individuals who will be found to not satisfy the classical criteria of CNSRD when follow-up studies are done in other years.

The reverse also is the case Section 5 1.2.2 showed that children with recurrent respiratory symptoms are not invariably included in a symptom-positive group in transversal studies when the questionnaire is used in medical history-taking.

In order to gain a better understanding of the significance of these findings, the following relationships were studied

6.2.1 *The relationship between the frequency of a positive symptom and the previous history of respiratory symptoms*

The findings are shown in Table 11

All symptoms are characterized by a marked, statistically significant ($P<0.01$ chi-square test) similarity between their appearance in one or several years of investigation and an affirmative answer to questions regarding the previous history As the number of cases in which a symptom is positive in more than two out of five years is small, it is difficult to decide whether a high incidence of symptoms is more frequently associated with a positive previous history than is a low incidence. This trend is undoubtedly present

The similarity between prolonged cough, dyspnoea on exertion and attacks of asthma on the one hand and periods marked by cough on the other is a very striking feature. This is also the case with previous histories of children with dyspnoea on exertion, attacks of asthma and wheezing and the similarity between histories of attacks of asthma and cough.

Conclusion. There is a statistically significant relationship between respiratory symptoms in children at school age and those appearing in previous years.

6.2.2. *The relationship between respiratory symptoms and the pulmonary function parameters one-second forced expiratory volume ($FEV_{1.0}$) and the forced expiratory volume expressed as a percentage of the vital capacity ($FEV_{1.0}$%).* (Tables 12 and 13)

The normal means shown in these tables for the $FEV_{1.0}$, i.e. the $FEV_{1.0}$(E) were calculated from the findings in the children without recent respiratory symptoms (D – C – c – w – n –) and with a negative previous history

The mean $FEV_{1.0}$% was 81 (±10 = 2SE). The figures listed in Table 13 were achieved by calculation of the mean pulmonary function values for each child from all measurements carried out during the course of the study (Children in whom less than three measure-

Text-table 4 *Analysis of variance of findings listed in Table 13*

Cough ≥ 3 months a year	Cough ≥ 3 consecutive months a year	Cough consecutive months a year	Cough 1 month a year	Dyspnoea on exertion	Asthmatic attacks	Rhinitis	D+C+ D+C− D−C+	D−C− and/or n and/or w+	D−C− c−n−w
$P = 0.01$	$P = 0.05$	$P = 0.05$	$P = 0.23$	$P < 0.01$	$P < 0.01$	$P < 0.01$	$P < 0.01$	$P = 0.37$	$P < 0.0$

ments were made, were not included in the tables.) The averages were then calculated from the individual averages in each group Comparison of the children with and without symptoms by age group (Table 12) shows that the mean $FEV_{1.0}$% is usually within one standard error of the normal mean (>76 percent) for all symptoms with the exception of asthmatic attacks. Children having asthmatic attacks show a mean $FEV_{1.0}$% within two standard errors of the normal mean up to the fourteenth and fifteenth years of life however the value decreases with increasing age. The mean FEV $_{.0}$% is slightly lower in children with symptoms than it is in those without. This is particularly true for asthmatic attacks. Table 13 shows the mean $FEV_{1.0}$% according to the number of years during which a symptom was positive

In the symptoms prolonged cough (three or more months a year three or more consecutive months a year two consecutive months a year), dyspnoea on exertion attacks of asthma and rhinitis as well as in the symptom-positive combinations, the mean $FEV_{1.0}$ and mean $FEV_{1.0}$% decrease as the number of years in which the symptom or combination of symptoms was present, increase This trend was verified by an analysis of variance (Text-table 4) The trend is significant for all symptoms except cough during one consecutive month. The fact that the symptom-negative combination with positive "secondary" symptoms (D–C– c and/or n and/or w+) does not show variations in pulmonary function indicates that the "secondary" symptoms are indeed of less importance than the major symptoms.

The fact that there is also a significant trend in rhinitis can be understood from Text-table 5, which shows that there is a relationship between the number of years in which rhinitis occurred and that in which other respiratory symptoms were present. This relationship is highly significant for all respiratory symptoms in this table ($P < 0.01$ chi-square test).

Conclusion A study of the relationship between various respiratory symptoms and the number of years for which they were present shows that the pulmonary function parameters which were measured decrease with the duration of the symptoms.

This supports the view that these symptoms are relevant as parameters of recurrent or chronic respiratory disorders in children. The effect can be seen already in children who have a major symptom for only one year and it is most marked in children with asthmatic attacks. Prolonged cough, dyspnoea on exertion and the

Text tab e *Percentage f children with rhinitis associated with other respiratory symptoms*

Rhinitis (years)	Cough ≥ 3 months year			Cough ≥ 3 consecutive months a year			Dyspnoea on exertion			Asthmatic attacks		
No. of years	0	1	≥ 2	0	1	≥ 2	0	1	≥ 2	0	1	≥ 2
0	90.0	8.3	1 7	97 1	2.3	0.6	34.1	8.3	7 6	95.3	4.1	0.6
1	50.0	31.3	18.8	6 5	30.0	7.5	57.5	16.2	26.3	87.5	8.8	3.3
	58.2	11 4	30.4	73 4	15.2	11 4	46.8	21.5	31.6	88 6	6.3	5 1

symptom-positive combinations show a similar pattern in this regard. This means that the symptoms referred to must be taken into account in estimating risks, when they have appeared at least once at school age (See also Section 7 4)

6.2.3 *The relationship between respiratory symptoms and the histamine threshold*

This is shown in Table 14 Only those children in whom at least three determinations of the histamine threshold were made are included in this table. Each child is arranged in the order of frequency of the various symptoms according to the median value of all histamine thresholds determined in that child.

The question as to whether there is a relationship between the median histamine threshold value and the presence of respiratory symptoms was studied. The relationship between a markedly reduced median value of the histamine threshold (<8 mg/ml) and the presence of symptoms for one or several years is highly significant for each individual symptom and for the symptom-positive combinations ($P < 0.01$ chi-square test). Because of insufficient numbers, this could not be examined for asthmatic attacks.

Conclusion. There is a statistically significant relationship between the presence of symptoms and a lowered histamine threshold. This also serves to support the relevance of the symptoms referred to as parameters of chronic or recurrent respiratory disorders in children. The question of whether a histamine threshold showing a permanent decrease has any prognostic significance (see also p. 24) cannot be answered because of the small number of children in whom this was the case. Follow-up studies in a selected population will be better suited for this purpose (26).

6.3 COMPARISON OF THE FINDINGS IN HOOGVLIET AND IJSSELMONDE IN RELATION TO AIR POLLUTION

Fig. 6 shows the mean monthly concentrations of sulphur dioxide and smoke in the two districts during the period from 1967 to 1972. As the determinations made in 1968 and the first half of 1969 were unreliable, these are not stated. Beginning in June 1969 air pollution was measured by a semiautomatic apparatus, the so-called merry-go-round. In view of the results of measurements in 1967 and previous years, it was believed that the concentrations of sulphur dioxide and smoke would be much higher in Hoogvliet than in IJsselmonde. However a chimney which is 213 m high has come into use at the Shell refinery at Hoogvliet in 1969 The differences in air pollution between the two districts turned therefore out to be relatively slight after 1969

In 1968, there was no appreciable difference in prevalence of symptoms between Hoogvliet and IJsselmonde. Also in the following years, there were no systematic or marked differences between the answers to the questions in the two districts. These answers therefore were not arranged by district in Tables 9–11

For a summary of the most important literature on the subject of air pollution and respiratory disease see Appendix IV

6.4 ALLERGY TESTS

The results of the first and second series of skin tests are listed for each birth cohort in Table 15*a*.

The proportion of children of the two birth cohorts in whom the tests were positive showed a two- to threefold increase where house dust, grass pollen and danders were concerned. It comes as no surprise that the proportion of positive tests in the youngest birth cohort in 1973 is of the same order of magnitude as that in the oldest birth cohort in 1968 and 1969 In fifty percent of the children in whom skin tests were positive in both series, the positive test was associated with a lower allergen concentration in the second than it was in the first series. Table 15*b* shows the symptom pattern of the children in whom skin tests were positive in 1973 and that of those in whom all tests were negative.

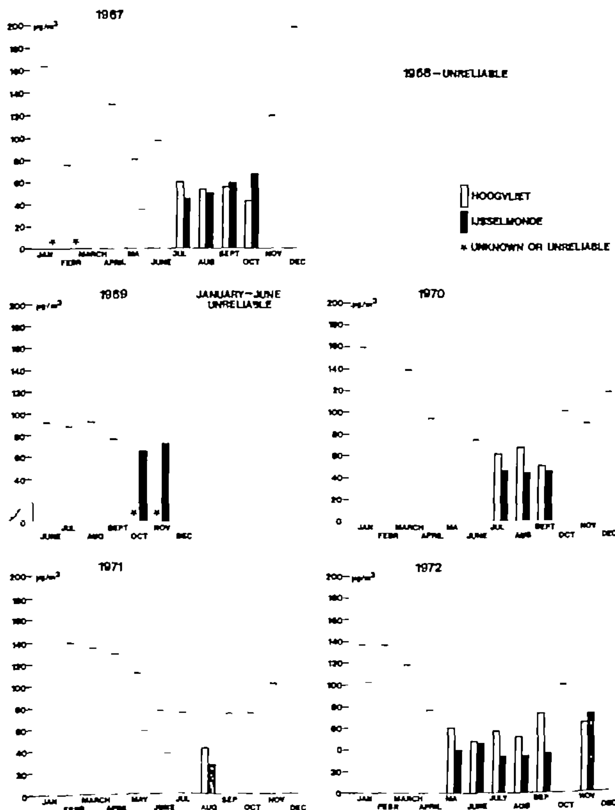


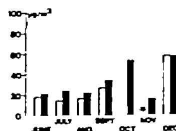
Fig. 6a. Mean concentrations of SO (µg/m³), Hoogvliet and IJsselmonde, 1967–1972.

1967

1968 – UNRELIABLE



1969 JANUARY JUNE UNRELIABLE



1970



1971



1972

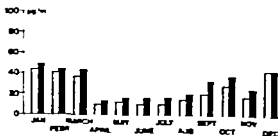


Fig 6b Mean concentrations of smoke (μg/m³), Hoogvliet and IJsselmonde, 1967–1972.

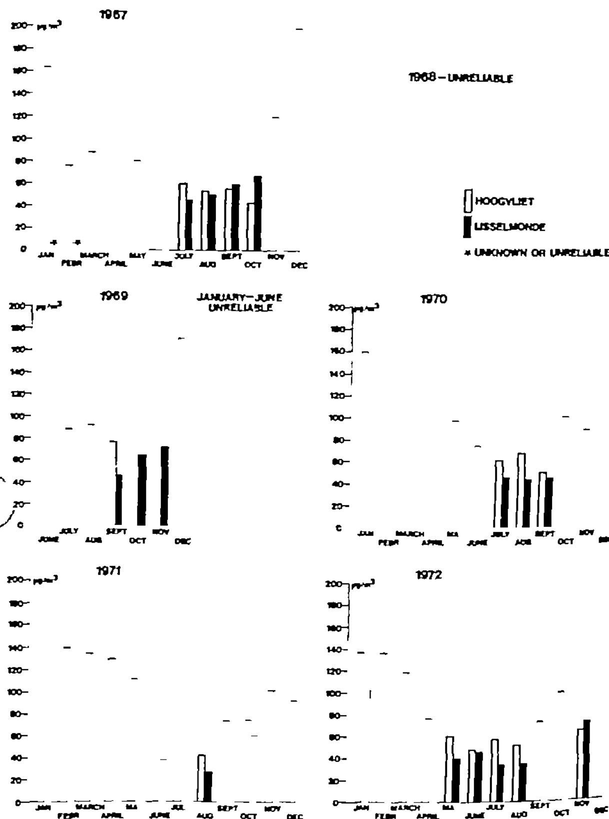


Fig. 6a. Mean concentrations of SO (μg/m³), Hoogvliet and IJsselmonde, 1967–1972.

1967

1968 – UNRELIABLE

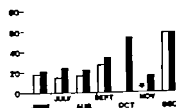


HOOGVLIET

IJSSELMONDE

* UNKNOWN OR UNRELIABLE

1969 JANUARY – JUNE UNRELIABLE



1970



1971



1972



Fig. 6b. Mean concentrations of smoke (µm/m³), Hoogvliet and IJsselmonde, 1967–1972.

gests that an affirmative answer should be rated as such This also holds true for the other major symptoms (cough for three or more consecutive months a year and asthmatic attacks) as well as for the questions cough for three or more months a year cough for two consecutive months a year and rhinitis. The last three symptoms were included in symptom group D−C− (c+w−n+) to make a differentiation possible between the CNSRD group according to the widely accepted criteria based on studies in adults (36) and symptoms or combinations of symptoms which may be of importance earlier in life. Exercise induced bronchial obstruction is a common symptom in children (20, 24 30). Unfortunately exercise tests using a treadmill or running to determine whether bronchial obstruction particularly occurs in the children with an affirmative answer to the questions on dyspnoea on exertion could not be performed.

Wheezing without prolonged cough, dyspnoea on exertion or asthmatic attacks does not affect pulmonary function. Wheezing has thererefore been classified among the minor symptoms.

Table 13 shows that the FEV_1% was a more ensitive parameter of *pulmonary function* than e FEV_1. This is in accordance with the findings reported by other investigators (22, 46).

In children with symptoms the decrease in pulmonary function was slight and also in those with symptoms for many years, the mean FEV_1% usually was within one standard error of the normal mean in all symptoms with the exception of attacks of asthma. This can be partly due to the fact that—in order to obtain beseline values—measurements were carried out only when respiratory symptoms were not present at the time of investigation and in a season in which few respiratory infections occurred.

Future surveys should include pulmonary function tests revealing changes in the small bronchi such as determination of the expiratory flow at small lung volumes and the closing volume (8, 16 35, 40, 41 55 56).

Section 5 1.2 shows that *observer s errors* (see also Appendix II) did not affect the answers to the questions to any appreciable extent. The reproducibility of the answers can be considered to be good The *histamine threshold* is usually regarded as a measure of reactivity of the respiratory tract to nonspecific stimuli (43 51) and as an endogenous characteristic of chronic nonspecific respiratory disease (52)

However as de Vries (52) has shown, in adults the histamine threshold is dependent of the initial pulmonary function. As this relationship was rather weak in the children studied, we continued to determine the histamine threshold each year and we have considered it to be an independent characteristic of CNSRD (see also Appendix III)

Surveys for CNSRD showed that a relationship between respiratory symptoms and a lowered histamine threshold (<16 mg/ml) was present in both adults (32) and children (29). Th findings in children were verified by the present study

As stated previously measurements were carried out only when respiratory symptoms were absent at the time of investigation. This enhances the value of the relationship found to exist between the histamine threshold and a history of respiratory symptoms in regard to the relevance of these symptoms as parameters of chronic or recurrent respiratory disorders.

It is still questionable whether a lowered histamine threshold can be considered as an endogenous characteristic of CNSRD Only 13 per cent of the children in this study showed a diminished median histamine threshold (<16 mg/ml) This is too small a number to answer this question

The prevalence of a lowered histamine threshold value varied considerably in the various years of investigation (Text-table 7).

This is more in favour of the histamine threshold to be a measure of the reactivity present at the time of investigation than to be an endogenous determined personal characteristic. This is also suggested by the findings in the Dutch alpine clinic for asthmatics in

Text-table 7 *Annual prevalence of histamine threshold*

Year of investigation	Histamine threshold (mg/ml) <8	16	>32 %
1968	5	14	81
1969	8	16	76
1970	1	9	90
1971	2	10	88
1972	4	7	89

Davos, where a lowered histamine threshold value is restored to normal levels in some patients, whereas it is not in others during their stay in the high mountains (25 26).

Patients were examined for the presence of *allergy* by intracutaneous skin tests in which various concentrations of allergen were used as recommended by Voorhorst (50). Some investigators claim that it is preferable to perform skin tests on the back, as the results obtained by this method are believed to be more sensitive and more readily reproducible This, however is denied by others (19).

For psychological reasons, the present tests were performed on the volar surface of the right forearm. We used the intracutaneous method since this is more sensitive than the prick test and since the test can be performed with various concentrations of a particular allergen. The fact that reagins to a specific allergen are present in the skin does not imply that bronchial obstruction will occur on inhalation of the allergen (1 28, 37)

In this survey we found a relationship between the presence of respiratory symptoms and positive skin tests, particularly to danders. This suggests that the increasing practice of keeping domestic animals in families and at schools may result in an increase in respiratory symptoms due to allergy to danders.

During the course of five years, the proportion of children with positive skin tests showed a two- to threefold increase with an increased intensity of the response This confirms the common finding that antibodies to allergens are to a large extent produced at primary and secondary school age.

Radiography was not found to be very useful in differentiating between children with and without respiratory symptoms. This finding is in accordance with that reported by Simon et al. (45). These investigators observed marked radiological changes only in children with severe or moderately severe asthma which continued to cause symptoms.

7.2. PREVALENCE

The prevalence rates listed in Tables 8 9*a*, 9*b* 9*c* 10*a* and 10*b* are based on the number of children of population A which took part in the study for a period of five years. The reasons for which children did not take part or no longer participated in the study are stated in section 4.3 These reasons did not include asthma, bronchitis or other respiratory conditions. In Table 20 the prevalence of symptoms in the children of population A in 1968 and 1972 is compared with that of the children who dropped out. The prevalence of symptoms during the last year in which these drop-outs took part in the study was that used in the table. The prevalence rates show only slight differences the prevalence of symptoms in those who dropped out is slightly lower than it is in those who took part for five years. These may therefore be regarded as a random sample of the children of the two birth cohorts living in Hoogvliet and IJsselmonde on October 1 1967 The symptom-positive groups include those children who satisfy the criteria of CNSRD applying to adults.

As has been mentioned earlier the effect of the symptoms cough for three or more months a year and two consecutive months a year on pulmonary function is comparable with that of cough for three or more consecutive months a year Tables 21 and 22 show the prevalence rates for the children of the symptom-positive groups when the criterion of cough + (C+) is altered from cough for three or more conse

cutive months a year to cough for three or more months a year and/or two or more consecutive months a year When these criteria are applied, prevalence increases by 3-4 percent in the two youngest groups and by 1–2 percent in the older groups. The percentage of children included in one of the symptom-positive groups for two or more consecutive years also shows a slight increase. The general prevalence pattern, however remains almost unchanged. This would not be the case if the symptom "wheezing" were to be added as a criterion for classification within one of the symptom-positive groups. The proportion of children which would then be included in these groups is much higher as is shown in Table 23 However as stated on p 18, "wheezing" may be regarded as a secondary symptom.

Although approximately 50 percent of the children of the oldest birth cohort turned out to be smokers at 14–16 years of age (Table 24) this does not affect the prevalence of symptoms in this cohort.

As stated previously the increase in the prevalence of the symptom-positive groups, which occurred in the 12th–13th year of life as compared with the previous year is caused by an increase in the symptom dyspnoea on exertion. This increase is unlikely to have been due to smoking.

The prevalence rates determined in the present study are comparable only in part with those recorded by Knol (29) as this author took the recent and previous histories into account in calculating prevalence The prevalence rates reported in the present paper were based only on recent histories. Comparison with the prevalence rates reported by others is not possible because of the differences in criteria as has been mentioned in the introduction.

7.3 RELATIONSHIP BETWEEN RESPIRATORY SYMPTOMS AND EXOGENOUS FACTORS

7.3 1 *Air pollution*

There was no difference between the prevalence of respiratory symptoms in Hoogvliet and that in IJsselmonde The anticipation, based on the results of measurements carried out in 1967 and previous years, that pollution by sulphur dioxide and smoke during the period of investigation would be much more marked in Hoogvliet than in IJsselmonde was not realized Therefore, it was not possible to determine whether the prevalence of prolonged cough or dyspnoea increases with the degree of air pollution.

Studies in other areas of the Netherlands (Westland, Zuid-Beveland) have shown that this is actually the case where cough is concerned (6 27) The problem of short-lived respiratory symptoms resulting from air pollution could not be examined in the present study

7.3.2. *Social and demographic factors*

It has been reported several times in the literature that respiratory symptoms become increasingly common in children as they live in worse social conditions (10 11 17).

In order to determine the effect of air pollution under the best possible conditions of life, the study was done in districts marked by an adequate social level. Section 6 6 shows that slight social differences do not affect the prevalence of respiratory symptoms. Providing optimum housing is essential to effective treatment and prevention of chronic or recurrent respiratory symptoms.

7.3.3 *Smoking*

Children of the youngest birth cohort may be assumed to be non-smokers. The proportion of children of the oldest birth cohort who stated in an inquiry that they regularly smoked cigarettes was 24 percent in 1970 51 percent in 1971 and 57 percent in 1972 (Table 24). As these statements were anonymous, the existence of a possible correlation between symptoms and cigarette smoking could not be examined However our results showed that the overall-prevalence of respiratory symptoms did not increase at the ages at which regular smoking starts. In accordance with the findings reported by Colley (14 15) and unlike those reported by a number of other investigators, there was no evidence

that so-called passive smoking due to parental smoking had any appreciable effect on the appearance of respiratory symptoms in schoolchildren. For a review of the literature on smoking and its effects on health in children, the reader is referred to Bewley et al. (4) and to Appendix V

7.3.4 *Respiratory symptoms in parents*

There is a definite relationship between respiratory symptoms in parents and those in children. This finding is also in accordance with that reported by Colley (14 15).

Smoking may be taken to cause an increase in respiratory symptoms in the parents and thus indirectly to affect the symptoms in the children. However repeated studies on the subject as well as a study of the relative contributions of endogenous (genetic) factors (2, 5 38) and exogenous factors are still required.

7.4 LONGITUDINAL TREND

The present study was designed to get an impression of the longitudinal trend of symptoms of CNSRD in each child on the basis of particular features. As was apparent from section 6.2.2, the symptoms will merely cause a slight average decrease in pulmonary function and the mean pulmonary function values usually are within two standard errors of the normal mean values. This means that the pulmonary function parameters adopted (FEV $_{1}$, FEV %) are less useful in estimating the trend in each individual than are the symptoms. This also holds true for the histamine threshold, skin allergy and X-rays.

Very few children were found to have shown a particular symptom for more than two years or to have belonged to one of the symptom-positive groups for more than two years. Table 25, however shows that the respiratory symptoms in a large proportion of these children were less marked in other years. It would therefore appear to be justifiable in principle to regard schoolchildren in whom symptoms of prolonged cough or dyspnoea occur even if only incidentally as individuals with "chronic" respiratory disease (which does not imply that this actually is the case with all of these children).

In this context, "chronic" only means that the symptoms recur but does not say anything of the frequency and severity of these symptoms. Although it could be of importance to determine these for reasons of prognosis (42), this cannot be done with the questionnaire used.

In the population studied therefore only qualitative measurements of respiratory symptoms were carried out. Only studies in populations followed from childhood up to adult life will be able to show whether any prognostic value can be attached to these measurements. Studies by Colley (12, 13) suggest that this is the case. As the period for which the populations were followed was only five years, it is not possible to form an opinion on this subject as a result of the present study

On the other hand, efforts were made to gain an impression of the extent to which the previous history is an important factor in the symptom pattern during the period of investigation. For this purpose, the number of times that questions on the previous history were answered in the affirmative or in the negative was studied with regard to the symptoms "cough for three or more months a year" "cough for three or more consecutive months a year" "cough for two consecutive months a year" "cough for one consecutive month a year" "dyspnoea on exertion" "asthmatic attacks" and "rhinitis"

For each of the above symptoms and for eight questions referring to the previous history the percentage of children answering in the affirmative was divided by that answering in the negative This quotient represents the relative risk that a symptom which occurred in the previous history will recur in the recent history (7). All of this is included in Table 26 which shows that respiratory symptoms at a young age involve an obvious risk of recurring later in life.

As stated in the introduction, a justifiable opinion on the future course of a "chronic" respiratory condition in the individual child usually cannot be formed. From the point of

view of prevention, it would therefore seem advisable to consider symptoms such as prolonged cough or dyspnoea (regardless of their severity or frequency) in all schoolchildren as potential "risks" of CNSRD in adult life.

This implies that adverse exogenous factors should be avoided wherever possible and that symptoms should be treated by the best possible method. This means in practice

(1) Prompt treatment of bronchial obstruction and respiratory infections, if necessary daily drug treatment and physical therapy

(2) Prevention of bronchial obstruction and respiratory infection by avoiding exogenous factors known to be liable to cause symptoms in a particular individual.

(3) Improving housing and adverse social and psychological conditions.

(4) Preventing the children from smoking by personal counseling and health education.

(5) Vocational guidance counseling on habits of life, etc. if required.

(6) Measles and influenza vaccination.

Controlled screening of children with "chronic" respiratory disease at primary and secondary schools by the school health officer would be advisable. This can be done by using a simple questionnaire. Experience elsewhere (27) showed that a brief questionnaire completed by the parents at home will usually serve the purpose.

Attending physicians (general practitioners as well as specialists) should be more keenly aware of the need for "preventive treatment" than they are today

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Text Questionnaire (continued)

	1968[a] Question number	1969–1972[b] Question number
Did your child have to stop regularly because of breathlessness and sit down when playing outdoors or walking up a staircase in winter?	—	17
Has your child ever been troubled by shortness of breath when playing outdoors or walking up a staircase in summer?	—	18
Has your child regularly been troubled by shortness of breath when playing outdoors or walking up a staircase in summer?	—	19
Did your child have to stop regularly because of breathlessness and sit down when playing outdoors or walking up a staircase in summer?	—	20
Has your child ever been troubled by shortness of breath when playing outdoors or walking up a staircase in the previous years?	—	21
At what age did you notice for the first time the breathlessness of your child? (Accept "around this age .)	18	22
IV *Wheezing*		
Did your child ever wheeze in the previous years?	19	—
Did your child ever wheeze during the past winter?	—	23
Did your child wheeze most days or nights in winter?	—	24
Did your child wheeze two times or more? (If "no proceed to *V Asthmatic attacks* if "yes proceed to the next question.)	20	—
Does your child wheeze most days or nights?	21	—
Did your child ever wheeze during the past summer?	—	25
Did your child wheeze most days or nights in summer?	—	26
Does your child wheeze all days or nights.	22	—
At hat age did your child start wheezing	23	—
V *Asthmatic attacks*		
When resting, did your child ever ha attacks of shortness of breath with wheezing (asthmatic attacks)	24	—
When resting, *did* your child ever have attacks of shortness of breath with wheezing (asthmatic attacks) in winter?	—	27
When resting, did your child ever have attacks of shortness of breath with wheezing (asthmatic attacks) in winter in the previous years?	—	28
When resting, did your child ever have attacks of shortness of breath with wheezing (asthmatic ttacks) in summer?	—	29
When resting, did your child ever have attacks of shortness of breath with wheezing (asthmatic ttacks) in summer in the previous years? (If no proceed to VI *Nasal catarrh* if "yes proceed to the next question.)	—	30
At what age did your child first have these attacks? (Accept "around this age".)	25	31
At what age did your child last hav these attacks. (Accept around this age".)	26	32
Is your child ever short of breath when resting?	27	—
VI. *Nasal catarrh*		
Did your child ever have stuffy or a running nose?	—	33
Has your child usually been troubled by stuffy nose or nasal catarrh?	29	—
Have these troubles been present on most days for as much as three or more consecutive months? a. in winter b. in summer	30	—
Has your child usually been troubled by a stuffy nose or nasal catarrh in the past winter?	—	34
Have these troubles been present on most days for as much as three or more consecutive months in winter?	—	35
Have these troubles been present on most days for as much as two consecutive months in winter?	—	36
Have these troubles been present on most days for as much as one month in winter?	—	37

Text Questionnaire (continued)

	1968[a] Question number	1969–1972[b] Question number
Has your child usually been troubled by a stuffy nose or nasal catarrh in the past summer?	—	38
Have these troubles been present on most days for as much as three or more consecutive months in summer?	—	39
Have these troubles been present on most days for as much as two consecutive months in summer?	—	40
Have these troubles been present on most days for as much as one consecutive month in summer?	—	41
VII. *Previous diseases*		
Did your child ever have:	36	47
Eczema?	36*a*	47*a*
The tonsils removed?	36*e*	47*e*
Attacks of bronchitis or asthma?	36*h*	47*h*
Periods of cough?	36*i*	47*i*
Pneumonia	36*j*	47*j*

Several investigations have been carr l) t r the comparability of medical histori ts b various interviewers in an epidem g a study

Cochrane and Chapman (1) differ n t be tween two potential types of error

1 Inter-observer's errors errors appearing as differences between the results obtained by investigators.

2 Intra-observer's errors errors appearing when the results obtained by a particular inter viewer are different when he repeats his study in the same individuals. This is due among other things, to the fact that one interview may affect the answers given during another inter view Kinsey et al. (4) therefore recommend an interval of at least eight months between two interviews of the same subject.

Cochrane and Chapman (1) had various interviewers question a large number of miners on respiratory and other symptoms. A stand ardized questionnaire was not used in this case, although efforts were made to standardize the technique of interviewing wherever possible in the survey

The results obtained by the interviewers showed marked differences as regards the symptoms cough, pain in the chest and dyspepsia. The answers to those questions which had previously been discussed and standardized by the interviewers among themselves (such as the question on exertional dyspnoea) showed less disagreement between the interviewers.

It is concluded by these authors that careful standardization of questions is a condition essential to obtaining comparable results.

Schilling et al. (6) studied medical history taking and physical examination by two physi cians who took turns in examining one half of a group of individuals at a four-month interval. They observed significant differences between the results obtained by the two investigators concerning the results of physical examination and those of history taking. They believe the differences in the results of history-taking to have been due to the following factors

1 A difference in the answers given to the same question by the interviewee.

2 The fact that the answer given was influenced by the interviewer

3 Different interpretations of the same answer by different interviewers (Standardization of answers does not ensure standardization of interpretation.)

Fairbairn, Wood and Fletcher (?) believe that the initial stages of chronic bronchitis can only be recognized by the medical history If the epidemiology of chronic bronchitis is to be studied, the results of various investigations will have to be comparable. Where medical histories are concerned, comparison will be possible only when a standardized question naire is used The authors carried out a survey in which a standardized questionnaire was employed by six different investigators three physicians and three health visitors distributed at random over the interviewees. This made it possible to compare the physicians and health visitors as groups and as individual investigators. The interviews were recorded on tapes and played back later The subjects interviewed were postmen and women sorters in London. They were unselected their ages ranged [illegible] rty to fifty-nine.

Two interviews were conducted at an interval of at least four weeks. Care was taken to prevent the interviewee from being interviewed twice by the same person. In four [illegible] there were significant differences among the physicians on the one hand and the health visitors on the other

In thirteen questions, there were [illegible] individual differences [illegible] the results [illegible] these, four were due to differences [illegible]

Arts Pathok S[illegible]

physicians the other nine were due to differences among the health visitors.

The differences concern only *affirmative* answers.

Among others, these differences were due to the following causes

(1) The same interviewees gave different answers to questions put in the same way by the two interviewers.

(2) The health visitors as a group more often rated vague answers as positive than did the physicians as a group

(3) When a question was answered in the negative, some interviewers asked questions which they should not have asked according to the protocol.

(4) The results suggested that questions which were not put clearly were occasionally answered in the affirmative, even though they had not been properly understood

(5) The speed with which the interview was conducted influenced the number of affirmative answers, particularly the answers to questions on the previous history of disease

(6) In a number of cases, the question stipu- [illegible] was asked in a different (suggestive) [illegible]

(This mistake was made particularly when the question was formulated in such a way that it was not easy to ask it in a natural manner)

(7) In three per cent of the cases, incorrect recording by the interviewer was the cause of the differences.

Causes of 149 differences in results in nine questions

Cause	Number	Percentage
Interviewer	93	62
Interviewee	32	21
Question	2[illegible]	16
	149	100

The differences wer caused by the inter viewers in 62 per cent of th cases this was mainly due to the fact ha hey did not stick to the literal wording of the question. As a re sult, an unduly large number of affirmative answers was obtained.

The difference between the two most experi enced interviewers was as large as that between any other pair of interviewers.

Several investigators (3) (5) (7) are engaged in developing other methods of medical history taking. The most recent procedure is a question-naire controlled by a computer

Questions appear on a screen the inter viewee selects one of four numbered answers yes, no I don't know I don t understand. He presses the corresponding button and, depending on his answer the computer will either proceed to the following general question or cause a more detailed question on the same subject or some further explanation to appear on the screen. This basic technique is currently being developed to a further extent, among others, by improving understanding and co-operation on the part of the interviewees. In the Mayo Clinic, for instance, the questions are illustrated by drawings. These methods may improve the possibilities of standardization. The answers are immediately ready for processing in the computer Drawbacks are the considerable expense, the fact that only a limited number of individuals can ben "interviewed" at the same time as well as the fact that errors cannot be traced to their source later on.

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APPENDIX III. HISTAMINE THRESHOLD AND INITIAL PULMONARY FUNCTION

INTRODUCTION

Many stimuli having a local action (pharmacological, physical, allergic stimuli) may cause swelling of the mucosa, hypersecretion and contraction of the smooth muscle tissues in the bronchi. The degree of "reactivity" will vary from one individual to another. The histamine threshold or acetylcholine threshold (the lowest concentration of histamine or acetylcholine resulting in a decrease of ≥15 per cent of the vital capacity or the one-second forced expiratory volume, or other measures of bronchial obstruction) are often adopted as parameters of this reactivity (3).

De Vries (4) pointed out that initial pulmonary function (measured as the one-second forced expiratory volume) and the histamine threshold are not independent of one another. He posed the question whether the histamine threshold may be regarded as a correct parameter of reactivity or whether it merely is an indirect measure of bronchial obstruction. He concluded that, rather than the histamine threshold as such, an index derived from it, the so-called reactivity score might provide a superior parameter of bronchial reactivity.

Cade and Pain (1) observed no relationship between the acetylcholine threshold and initial pulmonary function in asthmatic patients free of symptoms. During a symptom-free interval, the acetylcholine threshold was found to be constant over a period of a few weeks.

METHODS

The relationship between the histamine threshold (3) and the pulmonary function values one-second forced expiratory volume (FEV_1), peak expiratory flow (PEF) and vital capacity (VC) was studied in children with chronic nonspecific respiratory disease who attended the outpatient department for respiratory diseases of the Sophia Children's Hospital and in children who took part in the population survey. Follow-up studies were done in these children to determine whether any trend of the histamine threshold values in a particular child is reflected in a similar trend of the pulmonary



Fig. 1. Relationship between $FEV_1/FEV_{1(P)}$ and histamine threshold.

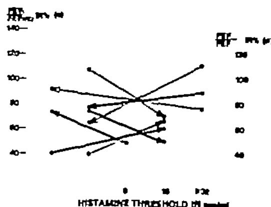


Fig. 2. Various relationships between pulmonary function and histamine threshold.

Table 1 *Correlation between histamine threshold and initial pulmonary function in children with chronic nonspecific respiratory disease*

Histamine threshold (mg/ml)	$FEV_1/FEV_{1(E)}$ Mean value	$FEV_1/FEV_{1(E)}$ Number examined	$VC/VC_{(E)}$ Mean value	$VC/VC_{(E)}$ Number examined	$PEF/PEF_{(E)}$ Mean value	$PEF/PEF_{(E)}$ Number examined
<	0.77	12	0.97	12	0.93	13
4	0.85	18	1.03	18	0.97	11
8	0.90	7	0.99	7	0.96	8
16	1.02	2	1.12	2	1.06	
≥32	0.93	11	0.96	11	1.18	18

(E) = height-adjusted mean value according to Polgar (2).

function values during the successive tests performed in that child. This was accomplished as follows. A score also used in Kendall's rank correlation test was calculated for each child per height-adjusted pulmonary function. For the relationship between the histamine threshold and $FEV_1/FEV_{1(E)}$, for instance, the following procedure was adopted

Initially those children in whom both the histamine threshold and the FEV_1 had been determined in more than one study were selected. All tests performed in these children were com- 1 in pairs. When two tests are performed, one paired comparison is possible (1→2, 1→3 2→3) when four tests are performed, six paired comparisons are possible, etc. A partial score which may assume the values −1 0 or +1 is added to each paired comparison. This partial score is calculated as follows

Histamine threshold higher in second test than in first test, $FEV_1/FEV_{1(E)}$ being also higher +1

Histamine threshold higher in second test than in first test but $FEV_1/FEV_{1(E)}$ lower than in first but FEV /FEV (E) lower −1

Histamine threshold lower in second test than in first test but FEV_1/FEV higher −1

Histamine threshold lower in second test than in first test, $FEV_{1,e}/FEV_{1,e}$ exp also lower +1

Histamine threshold and/or $FEV_{1,e}/FEV_{1,e}$ exp equal in the two tests 0

For this purpose, the histamine thresholds were classified into the following groups

≤4 8, 16 and ≥32 mg/ml. Two values of $FEV_{1,e}/FEV_{1,e}$ exp were regarded as being different as soon as they were unequal. Although a difference of two values, ranging from +5 per cent to −5 per cent, does not necessarily mean that there is an actual difference but may be due to variability in the measuring technique, every difference was regarded as an actual difference in calculating the partial score A longitudinal relationship if any will thus be more likely to be detected than it will when values differing from each other by less than 5 per cent are considered to be equal.

The total score of a child for the relationship

Table 2. *Correlation between histamine threshold and initial pulmonary function in a random population of 11 year-old boys and girls*

Histamine threshold (mg/ml)	$FEV_1/FEV_{1(E)}$ Mean value	$VC/VC_{(E)}$ Mean value	Number examined
≤ 4	0.85	0.96	6
8	0.86	0.90	16
16	0.94	0.96	7
≥32	0.93	0.95	32

See Table 1

$FEV_1/FEV_{1(E)}$ means one-sec o forced expiratory volume divided by the height adjusted mean one-second forced expiratory volume.

$PEF/PEF_{(E)}$ and $VC/VC_{(E)}$ ha a similar meaning. The height-adjusted mean values are according to Polgar (2).

between the histamine threshold and FEV_1/FEV_{100} exp. then will be the sum of the partial scores of all paired comparisons. When two tests have been performed in a child, the total score may therefore assume the values +1 0 or −1 When three tests have been performed, the total score may assume all the values from −3 up to and including +3 and it may assume all the values from −6 up to and including +6 in the event of four tests.

The same method was used in calculating the total scores of each child for the relationship between the histamine threshold and the $VC/VC_{(p)}$ exp and, if determined, for the relationship between the histamine threshold and the $PEF/PEF_{(p)}$.

RESULTS

(1) *Transversal study*

Tables 1 and 2 show the mean initial pulmonary function values for each histamine threshold. There is a linear relationship between the initial value of $FEV_1/FEV_{1(p)}$ or $PEF/PEF_{(p)}$ and the 2 logarithm of the histamine threshold, which is significant at the 5 per cent level test. This means that, starting from the null hypothesis that there is no relationship between the initial pulmonary function value and the histamine threshold, the likelihood that there is a linear trend such as that present in this case or that there is an even more marked linear trend will be smaller than or equal to 5 per cent. Therefore, the null hypothesis at a 5 per cent level has to be rejected. There is no such relationship between the VC and the histamine threshold

(2) *Longitudinal study*

The total scores per pulmonary function parameter for a number of the children listed in Tables 1 and 2 as well as for a number of other children are shown in Tables 3 and 4 In a large number of cases, this total score is found to be nil. As is shown by Tables 5 and 6, this is usually due to the fact that the value of the histamine threshold is identical in all studies. Therefore, it could not be concluded from these findings that, as a rule the trend of the histamine thresholds is identical with a similar trend of pulmonary function values during

Table 3 *Scores of histamine thresholds and initial pulmonary functions at repeated examinations children with CNSRD number of children*

	Number of examinations		
Score	2	3	4
$FEV_1/FEV_{1(p)}$			
−6			
−5			
+4			
−3		1	1
+		7	
+1	4	1	
0	13	19	
−1	9		
−2			
−3			
−4			
−5			
−6			
Total number of children	26	30	10
$VC/VC_{(p)}$			
+6			
+5			
+4			
+3			
+		8	1
+1	6	2	
0	14	17	7
−1	6	1	
−2		2	
−3			
−4			
−5			
−6			
Total number of children	26	30	10
$PEF/PEF_{(p)}$			
+6			
+5			
+4			
+3			
+2			
+1	14		
0	17		1
−1	16	1	
−2		1	
−3		1	
−4			
−5			
−6			
Total number of children	47	3	1

See Table 1.

Table 4 *Scores of histamine thresholds and initial pulmonary functions at repeated examinations in a random population of boys and girls 11–13 years of age number of children*

Score	Number of examinations 2	3	4
$FEV_1/FEV_{1(p)}$			
+6			
+5			
+4			2
+3		1	5
+2		2	
+1	4		2
0	15	6	17
−1	4	1	
−2			
−3			2
−4			
−5			
−6			
Total number of children	23	10	28
$VC/VC_{(p)}$			
+6			
+5			
+4			
+3		1	4
+2		1	1
+1	5		3
0	15	8	18
−1	3		
−2			2
−3			
−4			
−5			
−6			
Total number of children	23	10	28
$PEF/PEF_{(p)}$			
+6			
+5			
+4			
+3		1	
+		4	1
+1	5		
0	[illegible]	10	3
−1	5		1
−2		2	
−3			
−4			
−5			
−6			
Total number of children	32	19	5

See Table 1

successive studies. This similarity was therefore examined with regard to the VC and FEV_1 in twenty and with regard to the PEF in twenty-two children. The results are listed in Table 7 These show that there is usually an adequate relationship between the trend of pulmonary function values and that of the histamine threshold values in the children studied.

COMMENT AND CONCLUSIONS

Though significant, the relationship between the initial values of the $FEV_1/FEV_{1(p)}$ or PEF/ $PEF_{(p)}$ exp and the initial value of the histamine threshold is rather weak. This is also apparent from Figure 1 in which the initial values of the $FEV_1/FEV_{1(p)}$ of a number of children who took part in the population survey have been plotted against their histamine thresholds. When the histamine threshold of a child is given, the $FEV_1/FEV_{1(p)}$ cannot be even approximately predicted, nor can the histamine threshold of a child be

Table 5 *Number of children examined twice and scoring 0 CNSRD*

	Histamine threshold	Number
$FEV_1/FEV_{1(p)}$		
Higher	Equal	8
Equal	Higher	
Equal	Equal	
Equal	Lower	
Lower	Equal	5
Total		13
$VC/VC_{(p)}$		
Higher	Equal	6
Equal	Higher	
Equal	Equal	1
Equal	Lower	1
Lower	Equal	6
Total		14
$PEF/PEF_{(p)}$		
Higher	Equal	10
Equal	Higher	
Equal	Equal	
Equal	Lower	
Lower	Equal	7
Total		17

See T ble 1

Table 6 *Number of children examined twice and scoring 0 selected at random*

	Histamine threshold	Number
$FEV_1/FEV_{1(P)}$		
Higher	Equal	9
Equal	Higher	
Equal	Equal	1
Equal	Lower	
Lower	Equal	5
Total number		15
$VC/VC_{(P)}$		
Higher	Equal	8
Equal	Higher	
Equal	Equal	
Equal	Lower	
Lower	Equal	7
Total number		15
$PEF/PEF_{(P)}$		
Higher	Equal	10
Equal	Higher	
Equal	Equal	1
Equal	Lower	1
Lower	Equal	10
Total number		22

See T ble 1

predicted when its $FEV_1/FEV_{(P)}$ is known. The weakness of the relationship between the two quantities is also illustrated in the value for the coefficient of correlation of the $FEV_1/FEV_{(P)}$ and 2 log of the histamine threshold, viz., 0.32.

As is shown in a number of children in Figure 2, a child showing a histamine threshold which is twice or four times as high in a follow-up study as it was in the initial test may yet show a much lower $FEV_1/FEV_{1(P)}$ or $PEF/PEF_{(P)}$ and vice versa in the second study Table 7 shows that the trend of the $FEV_1/FEV_{(P)}$ was the reverse of that of the histamine threshold in eight out of twenty children and that the trend of the $PEF/PEF_{(P)}$ was the reverse of the histamine threshold in six out of twenty-two children. It would therefore appear justifiable to conclude that the histamine threshold value and the pulmonary function values measured in this study were mainly determined by different factors.

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Table 7 *Pulmonary function at first and second histamine threshold, children with CNSRD (number of children)*

	First histamine threshold compared with second histamine threshold								
	$VC/VC_{(P)}$			$FEV/FEV_{(P)}$			$PF/PF_{(P)}$		
	Higher	Equal	Lower	Higher	Equal	Lower	Higher	Equal	Lower
First histamine threshold at least steps lower than second threshold	6	0	3	4	0	5	4	0	8
First histamine threshold at least steps higher than second threshold	8	1	2	7	0	4	7	1	2

See T ble 1

1 INTRODUCTION

There is no consensus regarding the importance of air pollution as a factor in the pathogenesis and course of respiratory disease. A large number of investigators believe however that air pollution has an adverse effect.

Pollution of the outdoor air may be caused by:

(1) *Reducing substances* These mainly consist of sulphur compounds (sulphur dioxide sulphuric acid and sulphates), smoke and soot Reducing substances are believed to be the most injurious to health

(2) *Oxidizing substances* These mainly consist of hydrocarbons, nitrous oxide and photochemical reaction products (ozone aldehydes, ketones) Sunlight is required as a catalyst to produce these last named substances. Oxidizing substances cause irritation of the mucosae of the eyes, nose and throat in susceptible individuals. Although they may induce symptoms in subject with chronic respiratory disease, they apparently affect morbidity and mortality to a lesser extent than do reducing substances.

The air inhaled will be polluted for instance, by indoor factors under particular conditions of work, when the discharge of products of combustion in houses is inadequate and as a result of smoking. Studies on the effects of short and long-term exposure to polluted air on the respiratory system is numerous.

The present authors confine themselves to the most important studies on the subject For a comprehensive re iew of the literature readers are referred to he Air Pollution Abstracts (published by the National Air Pollution Control Association) a d Environmental Health published by Excer tr Medica.

The following ab e iations have been employed in the present p p r

PEF — peak (expiratory) flow
(F)VC — (forced) vital capacity
$FEV_{1.0}$ — one second forced expiratory volume
$FEV_{0.75}$ — identical with FEV_1 but 0 75 sec instead of one second

2. STUDIES ON THE SHORT TERM EFFECTS OF AIR POLLUTION

2.1 *In children*

Anderson and Larsen (1) studied nonattendance and the incidence of respiratory disease in children in the first form of the primary schools in three localities in British Columbia for a period of six monsths. Two of these localities were adjoining residential areas situated under the smoke of an industry: the third was a non-industrial residental area which was chosen because its climate was comparable with that of the other two Studies were made to deter mine whether the incidence of respiratory disease was higher in the two first-named areas. There was no significant difference in school absences among the three residential areas but respiratory infections and other forms of disease were more common and more prolonged in the children living in the polluted areas than they were in those living in the nonpolluted area peak flow values were also significantly lower in the children living in the polluted areas.

Lunn et al (20) studied 819 Sheffield infant school children living in districts in which the degree of air pollution (sulphur dioxide and smoke) differed widely Infections of the upper as well as those of the lower respiratory tract were found to be more common in the more polluted districts. Socioeconomic factors such as social class, size of the family and housing were of minor importance. Pulmonary function parameters ($FEV_{0.75}$ and FVC) were not

affected by socioeconomic factors or air pollution, except in the most severely polluted area, where these pulmonary function values showed a significant decrease. Four years later follow-up studies were done in 558 of these children at the age of 9 (21). Respiratory symptoms were less common than they had been four years previously and there were no longer any differences among the various residential districts. These improvements were accompanied by a decrease in the overall air pollution level in Sheffield and a reduction in the differences in air pollution among the districts themselves.

Girsh et al. (11) studied the relationship between weather conditions and air pollution on the one hand and peaks in the incidence of attacks of asthma on the other by recording the number of patients with attacks of asthma attending the out patient department of a Philadelphia children's hospital daily for two years. This number was three times as high on days marked by a measurable increase in air pollution (sulphur dioxide, nitrous oxide, carbon monoxide and soot). Attacks of asthma were four times as common on days marked by a high atmospheric pressure as they were on days marked by a low atmospheric pressure. During the period of investigation, high atmospheric pressure accompanied by increased air pollution was present on 117 days. The incidence of attacks of asthma on these days showed a ninefold increase compared with that on days on which the air was cleaner and less stagnant.

Ferris (9) studied school absences in approximately 700 first and second graders of seven primary schools in Berlin (New Hampshire) over a period of eighteen months. The schools were situated in areas in which air pollution (sulphur dioxide and smoke) differed markedly. Differences in school absence were not observed. However the PEF, FVC and FEV values measured during the second period of investigation were significantly higher than were those in children of schools in the nonpolluted districts. This was not adequately accounted for by differences in social class. The author believes that the differences in pulmonary function values may have been due to differences in air pollution (see also 24).

Chiaramonte et al. (5) studied 429 children attending the emergency room in the children's ward of Long Island College Hospital, New York for three weeks, which included a few days with a marked increase in air pollution (sulphur dioxide). Eighty-three of these children showed respiratory conditions: the majority were hospitalized during or just after the period of air pollution. The number of children admitted for obstructive respiratory disease was larger during or just after the air pollution peak than it was during the other periods. The differences were statistically significant.

McMillan et al. (22) studied pulmonary function in third graders of two primary schools in two towns marked by different degrees of air pollution (sulphur dioxide, nitrous oxide, soot). Pulmonary function values (PEF) were measured by a peak-flow meter twice monthly for eleven months, invariably at 1 p.m., the time at which the concentration of oxidant air pollution was believed to be highest. The studies were done to examine whether:

(1) Sudden changes in oxidant air pollution are associated with changes in PEF. There was no evidence to suggest that this was so. There was a constant difference between the mean PEF in the children of the two schools but a decrease in mean PEF was not associated with an increase in air pollution in either of the two groups.

(2) Prolonged exposure to air pollution is associated with a permanent decrease in PEF. The mean PEF in the children attending the school in the most severely polluted area was found to be constantly higher than it was in those attending the school in the less severely polluted area.

(3) Symptoms of infection of the upper respiratory tract are associated with prolonged exposure to air pollution. The incidence of infection of the upper respiratory tract was almost three times as high in children attending the school in the less severely polluted area.

2.2. *In adults*

Lawther et al. (17) studied the relationship between respiratory symptoms and air pollution in cases of chronic bronchitis in London by having the patients record their symptoms every day The sulphur dioxide and smoke concentrations were measured at seven points in Inner London the patients all lived or worked in Greater London In 1959–1960 a positive relationship between air pollution and an increase in symptoms during the early part of the winter was found (November). This relationship was no longer present at the end of the winter (February). This survey which was carried out for the first time during the winter of 1954 to 1955 is now being repeated in London every five years.

For a period of six months, *Shy* et al. (24) studied the incidence of acute respiratory disease in families having a child attending an elementary school as a second grader The studies were done in four districts of Greater Chattanooga one in which air pollution by nitrous oxide was very severe, another which was polluted by particles floating high in the air and two "clean areas. More cases of respiratory isease were constantly observed in the two irst named areas, particularly during the out break of influenza A2. This difference in the incidence of acute respiratory disease in the various areas could not be accounted for by the family constellation or social class.

As part of a triennial follow-up study of the populations of Vlagtwedde and Vlaardingen, *Van der Lende* et al. (18) studied the VC and FEV $_{.8}$ in Vlaardingen during a short period of increased air pollution in October 1969 and compared the findings with those during a period of low air pollution. They observed a transient decrease in VC and $FEV_{1.0}$ during this period. These authors conclude that spirometry probably is a more sensitive method than medical history-taking in measuring the effects of air pollution peaks.

3 STUDIES ON THE LONG-TERM EFFECTS OF AIR POLLUTION

3.1 *In children*

Douglas and *Waller* (8) studied 3 866 children from birth in 1946 up to the age of 15 (1961). These children had been living in 2 689 different residential areas since their birth Each of these residential areas was classified into one of four categories according to the degree of air pollution (sulphur dioxide and smoke) The results were simple and constant in character conditions of the upper respiratory tract were not affected by the degree of air pollution but the incidence and severity of diseases of the lower respiratory tract were greater in those areas in which air pollution was more severe. This correlation was present at every age. There was no difference between the sexes or between different social classes.

Biersteker (3) observed no difference between the height adjusted mean peak flow rate in 500 Rotterdam school children living in a central district in which air pollution (sulphur dioxide and smoke) was relatively severe and that in 500 school children living in a nonpolluted suburban district.

Holland et al. (13) studied 10 971 children in four Kent districts showing various degrees of air pollution (sulphur dioxide and smoke). The mean PEF in children living in the most severely polluted area was lower than that in children living in the less severely polluted areas. This was independent of social class, size of the family and previous respiratory disease (which also was a factor in itself) It is concluded from these findings that air pollution probably results in changes in the respiratory tract during childhood These changes possibly continue to be present throughout life and may contribute to the subsequent development in chronic respiratory disease

Shy et al. (24), who studied second graders in four districts of Greater Chattanooga marked by different degrees of air pollution (nitrous oxide) found the $FEV_{0.75}$ to be lower in children in the district showing the highest degree of

hama produced larger quantities of sputum and more frequently showed chronic cough and irritation of the throat. Of these, cigarette smokers and subjects having previous histories of allergy showed the largest number of symptoms. The mean FVC was lower in the inhabitants of this area than it was in the inhabitants of Niigata, and this was particularly so in those who had been living in Tokyo and Yokohama for a considerable period.

Holland and *Reid* (14) studied the incidence of respiratory symptoms, sputum production and pulmonary function ($FEV_{1.0}$ and PEF) in the drivers of mail and delivery vans in the city of London and the towns of Gloucester Peter borough and Norwich. Particularly from the age of fifty symptoms were more common and more severe in the Londoners they produced larger average quantities of sputum and showed lower mean pulmonary function values. There was a definite relationship between personal smoking habits and the incidence and severity of the symptoms in each population studied. However the difference between urban and rural smoking habits failed to account for the higher incidence of respiratory symptoms in London. It is concluded by the authors that this higher incidence of symptoms was due mainly to the difference in air pollution (sulphur dioxide) between central London and the three country towns.

Biersteker (2) examined 1 000 Rotterdam municipal officers for symptoms of bronchitis. He observed a number of subjects showing bronchitis, the number increased with age. Those affected with bronchitis smoked a significantly larger number of cigarettes than did those free of bronchitis. The average period for which they had been living in Rotter dam (adopted as a measure of exposure to air pollution) did not differ in those with and those without symptoms.

Lambert and *Reid* (16) studied ... of respiratory disease in 9 975 ... in the 35–69 year range using a ... naire Chronic respiratory symptoms ... to be more common in smokers and to i...

with age. Men showed symptoms more frequently than women (both smokers and non smokers). The differences between urban and rural areas were not solely accounted for by differences in smoking habits. Air pollution (sulphur dioxide and smoke), however apparently did not affect nonsmokers to an appreciable extent. There seems to be an interaction between smoking and air pollution, resulting in an increased prevalence of respiratory disease in smokers living in highly polluted areas. This becomes particularly apparent with increasing age.

Cohen et al. (6) studied the incidence of cough, sputum production and a number of pulmonary function parameters in two comparable groups of nonsmoking adults permanently exposed to identical mean but different peak degrees of air pollution (sulphur dioxide, nitrates, sulphates). There were no significant differences between the two groups.

Ferris et al. (10) reported the results of a follow up study of adults in Berlin, Ne ... ampshire, in 1961 and 1967 Even when ... of ageing and changes in smoking ... taken into account ... f respir... were found to be ... on ... fact that the ... function studi... were superior ... accordance ... (sulphur dio... in 1967 than ... that this a... dence of re... in pulmo...

Since l... doing co... incidence ... disease a... (Vlagtwe... (Vlaard... oxide,

as well as dyspnoea is higher in smokers than it is in nonsmokers and it is also higher in the inhabitants of Vlaardingen than it is in those of Vlagtwedde. The $FEV_{1.0}$ showed few differences between smokers and nonsmokers and between the inhabitants of Vlaardingen and those of Vlagtwedde.

Conclusion

The data currently available in the literature on the relationship between air pollution and the incidence of respiratory disease are not in accord with one another. This is due among other things, to the fact that it is difficult to adequately differentiate between the effect of concurrent other provocative factors and that of air pollution. The relationship between air pollution and meteorological factors or the climate interferes with many studies on the short term effects of air pollution. In certain weather conditions which may induce respiratory symptoms (such as the concurrent presence of fog, a calm and sunlight), pollutant particles will not be dispersed but will continue to float over a particular area so that it *will be hard to deter*mine which is the (main) cause of an increase in respiratory symptoms. The problems relating to this matter have been described by Cassell et al. (4), among others.

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APPENDIX V EFFECT OF PARENTAL SMOKING ON RESPIRATORY SYMPTOMS IN THEIR CHILDREN

Various studies have been conducted on the effects of parental smoking on respiratory symptoms in children.

Cameron (1) made a telephone inquiry into the relationship between disease during the week prior to the inquiry and smoking by members of the family in 1 000 families in Denver. The number of patients among smokers and nonsmokers was equal in individuals over nineteen. In those under nineteen, the proportion of patients in smoking families was larger than that in nonsmoking families.

Cameron et al. (2) carried out a similar telephone inquiry on smoking habits and disease in 1 000 families in Detroit. They learned that respiratory disease was more common in 0–16-year-old children of smoking families than it was in children of nonsmoking families. This difference was not statistically significant in children under five. The amount of smoke to which the children were exposed in smoking families of sick children was larger than it was in smoking families in which the children were not ill.

Norman-Taylor (3) studied the relationship between respiratory infection and parental smoking habits in five year-old children. In nonsmoking families, 33.5 per cent of the children showed respiratory symptoms. In those families which included heavy smokers (one or several individuals smoking over twenty cigarettes daily), this proportion was 44.5 per cent.

Colley (4) examined the relationship between coughing in children in the 6 to 14 year range and parental smoking habits. The number of coughing children was smallest in nonsmoking parents and largest when the two parents smoked. Independently of parental smoking habits, there was a definite relationship between respiratory symptoms in the parents (in which expectoration on arising was adopted as a criterion) and constant coughing in the children. The number of coughing children of smoking parents without respiratory symptoms was only slightly larger than that of nonsmoking parents without respiratory symptoms. The results were obtained by questionnaires completed by the parents.

Colley et al. (5) did follow-up studies in 2 205 children in North-West London the studies started in the first year of life and were continued over a five-year period. Inquiries were made each year regarding pneumonia and bronchitis in the children and smoking habits and respiratory symptoms in the parents. During the first year of life, there was a relationship between the symptoms shown by the children and parental smoking. Bronchitis and pneumonia were more common in children of smoking parents than they were in children of nonsmoking parents. This relationship was absent in children after the first year of life. On the other hand, there was a correlation between respiratory symptoms in the parents (expectoration on arising being adopted as a criterion) and bronchitis and pneumonia in the children. In the first year of life, the hazard of bronchitis and pneumonia in the children was doubled by parental smoking.

O'Connell et al. (6) studied the effect of cigarette-smoke on asthma in children. For this purpose, a group of asthmatic patients was compared with a group of controls. Sixty per cent of the parents of the patients were smokers, as was also the case with 60 per cent of the parents of the controls. Smoke caused aggravation of the asthma in 26 per cent of the patients whose parents did not and in 67 per cent of those whose parents did smoke. In the controls smoke was experienced as an irritant of the respiratory tract by 2 per cent of the children whose parents

did not and by 16 per cent of those whose parents did smoke. Of the asthmatic children of non-smoking parents, 2 per cent showed an exacerbation of symptoms after inhaling cigarette smoke. This was the case with 16 per cent of the asthmatic children who had a single smoking parent and with 20 per cent of those who had two smoking parents. A considerable proportion of those asthmatic children whose symptoms were aggravated by cigarette smoke showed fewer symptoms when the parents gave up smoking.

Harlap et al. (7) did a prospective study of the number of admissions during the first year of life in children of mothers with known smoking habits. Children of smoking mothers were hospitalized more frequently than were those of non-smoking mothers. Admissions for bronchitis and pneumonia were significantly more common in children of smoking mothers than they were in children of nonsmoking mothers. This was only found to be the case with children from 6 to 9 months of age.

CONCLUSION

The studies of the relationship between parental smoking and respiratory disease in children showed that

(1) The effect of parental smoking on respiratory symptoms in children cannot be considered without paying attention to parental symptoms. A differentiation should be made between the effect of parental respiratory symptoms on the children through genetic factors and cross infection and the effect of cigarette smoke.

(2) Symptoms of asthma induced in children by smoke are aggravated more often when the parents are smokers than when they are non-smokers.

(3) The degree of sensitivity to cigarette smoke probably varies with age

(4) The amount of smoke inhaled has an effect on the symptoms.

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APPENDIX VI TABLES 1–26

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Table 1 *Sick absence comparison of chronic and acute conditions The Netherlands 1966 1963 1958*

	Numbers of I.S.C.[b]	1966 % of total number of days of absence	Average duration per spell of absence (days) M	F
Chronic diseases				
Cardiovascular diseases	410–416			
Diseases of endo-myo- or pericardium	420–422, 430–432	6.9	167 1	129 1
Disturbances in rate and rhythm	434	0.3	68.2	68.2
Other heart diseases		0.3	104 2	78.3
Hypertension and arteriosclerosis		*2.6*	*114 4*	*89.2*
Other diseases of the arteries		0.6	139 1	69.6
Total		10.7	118.6	86.9
Respiratory diseases	502, 526			
Chronic bronchitis emphysema, bronchiectasis	241 317 0, 510, 512, 522,	4.0	73 7	29 7
Asthma	525, 527 583	1.5	42.4	32.6
Other chronic respiratory diseases (excluded pneumoconiosis)	(783.0 excl.)	1 1	20.5	17.6
Total		6.6	45.5	26.6
Chronic arthritis and arthrosis	722 725	5 6	102.2	112.2
Ulcer of stomach and duodenum	540–542	5.0	55.5	55 6
Displacement of intervertebral disc	735	4.3	95.8	103.6
Acute diseases				
Psychoneurotic disorders	310–314, 317 5, 318, 354, 780, 6, 790, 791	16.8	34.4	30.3
Respiratory diseases	051 470–475, 480–483, 490–493, 500, 501 511 783, 0	34 4	11.8	10.0
Gastrointestinal diseases (excl. appendicitis)	048, 049 543 544, 570, 571 576	7.2	14.2	12.0
Accidents	742, N800–N999	13.7	24.6	25.9

Insured population of Trade Associations.

[b] I.S.C. = International Statistical Classification of Diseases Injuries and Causes of Death.

1963			1958		
of total number of days of absence	Average duration per spell of absence (days)		% of total number of days of absence	Average duration per spell of absence (days)	
	M	F		M	F
7.3	152.8	145.5	6.2	138.4	125.7
0.3	63.9	50.9	0.3	56.1	49.9
0.3	88.7	56.5	0.2	60.3	67.0
2 6	113.9	92.1	2.5	106.5	92.1
0.5	115.8	31.8	0.4	112.9	41.6
11.0	107.0	75.4	9 6	94.8	75.3
4.3	75.9	30.6	3.8	58.7	[illegible]
1.9	43.1	32.9	2.5	34.9	26.6
0.9	23.0	18.5	0.9	24.6	17.0
7 1	47.3	27.3	7.2	39 4	22.3
5.6	93.1	105.9	6.1	92.2	98.5
5.0	54.5	51.6	7.2	53.6	54.2
4.5	83 1	97.9	5.3	79.3	94.7
13.8	31.2	27 4	10.7	26.6	24 5
37.5	13.1	10.4	37.8	11 7	9.9
7.6	14.1	11 7	6.2	13.0	11.2
14.4	25 4	26.1	11 4	23.6	23 7

Table 2. *Mortality from asthma*[a] *and chronic bronchitis*[b] *males and females, per 100 000 of each age group 1959–1971 the Netherlands*

From. The International Statistical Classification of *Diseases, Injuries and Causes of Death.*

Year	Age (years) <20	20–39
1959	0.2	1.1
1960	0.2	1.4
1961	0.2	1.0
1962	0.2	0.9
1963	0.2	1.2
1964	0.2	1.1
1965	0.2	1.1
1966	0.3	0.9
1967	0.3	1 7
1968	0.2	1.0
1969	0.3	1.1
1970	0.1	0.4
1971	0.3	0.6

[a] Number 241 (−1968), 493 (1969+).
[b] Number 491 (−1968), 502 (1969+).

Table 3 *Attendance rate 1968–1972*

Year	Attendance popul. A (%)	Attendance popul. B[a] (%)
1968	70.6	
1969	90.4	75.0
1970	92.0	85.4
1971	98.2	97.5
1972	94.0	96.2
All years	58.3	60.0

Attendants are equally divided over areas, birth cohorts and sexes.

Table 4 *Number and percentage of positive and negative answers, per question*

Question (1968)	*Hoogvliet, Number 622* Yes	No	Unknown	*IJsselmonde, Number 630* Yes	No	Unknown
3 Did your child cough like this on most days for as much as three or more months a year?	46 (*7*)	573 (*92*)	3	45 (*7*)	584 (*93*)	1
4. Did your child cough like this on most days in winter for as much as three or more consecutive months?	4 (*4*)	595 (*96*)	3	19 (*3*)	611 (*97*)	
5. Did your child cough like this on most days in summer for as much as three or more consecutive months?	6 (*1*)	613 (*99*)	3	3 (*1*)	627 (*99*)	

In parenthesis: in of total.

Table 5 *Answer to question 36a (1968), 47a (1969). (Did your child ever suffer from eczema), 1968–1969*

Group	*p*	*P*	π	Number investigated
1 1	0.051	0.004	0.019	274
1 3[a]	0.025	0.004	0.060	341
1	0.084	0.005	0.033	203
3	0.087	0.027	0.034	237

In 1968 interviewer 1 in 1969 interviewer 1
In 1968 interviewer 1 in 1969 interviewer 3 etc.

Table 6. *Answer to question 36e (1968), 47e (1969). (Have the tonsils been removed), 1968–1969*

Group	*p*	*P*	π	Number investigated
1 1	0.535	0.008	0.079	275
1 3	0.569	0.004	0.107	41
1	0.598	0.000	0.049	204
2 3	0.524	0.013	0.064	237

In 1969 interviewer 1 in 1969 interviewer 1
In 1968 interviewer 1 in 1969 interviewer 3, etc.

Table 7 *Reproducibility of histamine thresholds (mg/ml), 1968–1970*[a]

1968	1969 <8	1969 16 + ≥3	Total number
<8, mg/ml	6	4	10
16 + ≥32, mg/ml	12	184	196
Total number	18	188	206

1968	1970 <8	1970 16 + ≥32	Total number
<8, mg/ml	2	8	10
16 + ≥32, mg/ml	1	166	167
Total number	3	174	177

1969	1970 <8	1970 16 + >32	Total number
<8, mg/ml	7	48	55
16 + >32, mg/ml	3	661	664
Total number	10	709	719

[a] Measurements in May–June of each year

Table 8. *Number of children investigated according to birth-cohort sex and symptom group 1968–1972 (population A)*

Dyspnoea + Cough + c+w+n+ see text page 15

Birth cohort	Sex	Dyspnoea + Cough +	Dyspnoea + Cough −	Dyspnoea − Cough +	Dyspnoea − Cough − c+w+ n+	c+w− n+	c+w+ n−	c+w− n−	c−w+ n+	c−w− n+	c−w+ n−	c−w− n−	Un-known	Total
1968														
1/10/60	M	6	13	8	6	6	5	5	2	29	4	130	0	214
30/9/61	F	1	11	9	3	2	0	9	1	22	3	152	1	214
Total		7	24	17	9	8	5	14	3	51	7	282	1	428
1/10/55	M	2	13	0	1	3	1	2	1	19	2	145	1	190
30/9/56	F	2	6	4	0	1	2	2	0	18	3	161	0	199
Total		4	19	4	1	4	3	4	1	37	5	306	1	389
Total general		11	43	21	10	12	8	18	4	88	12	588	2	817
In of total general		1.3	5.3	2.6	1.2	1.5	1.0	2.2	0.5	10.8	1.5	71.9	0.2	100
1969														
1/10/60	M	2	19	4	2	4	3	4	4	20	10	141	1	214
30/9/61	F	0	16	4	1	5	1	10	0	23	3	151	0	214
Total		2	35	8	3	9	4	14	4	43	13	292	1	428
1/10/55	M	2	24	0	0	2	1	2	1	13	4	141	0	190
30/9/56	F	3	25	0	0	5	0	4	1	15	2	143	1	199
Total		5	49	0	0	7	1	6	2	28	6	284	1	389
Total general		7	84	8	3	16	5	20	6	71	19	576	2	817
In of total general		0.9	10.3	1.0	0.3	2.0	0.6	2.4	0.7	8.7	2.3	70.6	0.2	100
1970														
1/10/60	M	3	23	2	2	2	1	4	4	24	6	143	0	214
30/9/61	F	3	10	1	0	5	2	2	4	24	6	157	0	214
Total		6	33	3	2	7	3	6	8	48	12	300	0	428
1/10/55	M	3	23	1	1	1	0	7	1	17	5	129	2	190
30/9/56	F	0	18	0	1	3	0	2	1	20	5	149	0	199
Total		3	41	1	2	4	0	9	2	37	10	278	2	389
Total general		9	74	4	4	11	3	15	10	85	22	578	2	817
I % of total general		1.1	9.1	0.5	0.5	1.3	0.3	1.8	1.2	10.4	2.7	70.9	0.2	100

1971														
1/10/60 – 30/9/61	M	5	20	3	1	1	2	5	5	15	7	146	4	214
	F	2	17	1	1	8	3	3	1	13	2	163	0	214
Total		7	37	4	2	9	5	8	6	28	9	309	4	428
1/10/55 – 30/9/56	M	1	19	1	1	2	1	3	0	10	5	144	3	190
	F	0	27	1	0	7	1	3	1	12	1	144	2	199
Total		1	46	2	1	9	2	6	1	22	6	288	5	389
Total general		8	83	6	3	18	7	14	7	50	15	597	9	817
In % of total general		1.0	10.2	0.7	0.3	2.2	0.9	1.7	0.9	6.1	1.8	73.1	1.1	100
1972														
1/10/60 – 30/9/61	M	3	16	4	1	3	0	1	6	15	9	153	3	214
	F	0	11	3	2	3	0	3	2	17	6	163	4	214
Total		3	27	7	3	6	0	4	8	32	15	316	7	428
1/10/55 – 30/9/56	M	2	12	3	0	2	0	2	2	10	8	149	0	190
	F	0	19	2	0	5	1	1	1	15	0	150	5	199
Total		2	31	5	0	7	1	3	3	25	8	299	5	389
Total general		5	58	12	3	13	1	7	11	57	23	615	12	817
In % of total general		0.6	7.1	1.5	0.3	1.6	0.1	0.9	1.3	7.0	2.8	75.3	1.5	100

Table 9c. *Percentage of children with cough, breathlessness on exertion asthmatic attacks, rhinitis, and in symptom positive groups according to age (population A)*

Age (years)	Cough >3 months a year	Cough >3 consec. months a year	Cough 2 consec. months a year	Cough 1 consec. month a year	Dyspnoea on exertion	Asthmatic attacks	Rhinitis	D+ C+ D+ C− D− D+
6/7	12.1	5.6	—	—	4.0	3.7	12.3	11.2
7/8	6.3	2.1	4.4	8.6	8.4	0.4	9.9	10.5
8/9	4.4	2.1	3.2	7.0	8.9	0.7	9.7	9.8
9/10	4.2	2.5	4.9	8.8	10.6	0.7	8.5	11.2
10/11	3.5	2.3	2.5	5.1	6.3	1.1	6.1	8.6
11/12	4.3	2.0	—	—	4.4	3.1	4.6	6.9
12/13	2.0	1.3	2.0	4.3	13.5	1.8	4.4	13.9
13/14	3.0	1.0	1.8	6.6	11.1	1.3	5.7	11.6
14/15	2.8	0.7	1.8	5.4	12.2	0.7	3.4	12.6
15/16	3.6	1.8	2.3	4.8	8.0	0.2	5.9	9.8
Number 6/11	428	428	428	428	424	426	422	428
Number 11/16	389	389	389	389	385	386	384	389
Total number all ages	817	817	817	817	809	812	806	817

See text p. 15.

Table 10a. *Number and percentage of children, according to the number of years with a positive item, per item and birth cohort (population A)*

In parenthesis, % of total number. Total numbers differ because of unknown or unreliable answers in some items.

Cough[a]

Number of years positive	Birth cohort 1/10/60–30/9/61				Birth cohort 1/10/55–30/9/56			
	>3 months a year	>3 consec. months a year	2 consec. months a year	1 consec. month a year	>3 months a year	>3 consec. months a year	2 consec. months a year	1 consec. month a year
0	344 (*80.3*)	381 (*89.0*)	405 (*94.6*)	374 (*87.4*)	346 (*88.9*)	370 (*95.1*)	377 (*96.9*)	345 (*88.6*)
1	54 (*12.6*)	33 (*7.7*)	21 (*4.9*)	49 (*11.4*)	31 (*7.9*)	14 (*3.6*)	12 (*3.0*)	38 (*9.7*)
2	17 (*3.9*)	12 (*2.8*)	2 (*0.4*)	2 (*0.4*)	7 (*1.8*)	4 (*1.0*)	0	5 (*1.3*)
3	10 (*2.3*)	1 (*0.2*)	0	3 (*0.7*)	4 (*1.0*)	0	0	0
4	2 (*0.4*)	1 (*0.2*)	0	0	0	0	0	1 (*0.2*)
5	1 (*0.2*)	0			1 (*0.2*)	1 (*0.2*)		
Total number	428	428	428	428	389	389	389	389

[a] Criteria see Table 9a.

Table 10*b* *Number and percentage of children according to number of years with symptoms birth cohort and sex (population A)*

Number of years positive	Birth cohort 1/10/60–30/9/61						Birth cohort 1/10/55–30/9/56					
	Boys		Girls		Boys + girls		Boys		Girls		Boys + girls	
	N	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%
0	154	71.9	167	78.0	321	75.0	146	76.8	150	75.4	296	76.1
1	30	14.0	23	10.7	53	12.4	17	8.9	20	10.0	37	9.5
2	9	4.2	13	6.1	22	5.1	8	4.2	14	7.0	22	5.6
3	8	3.7	5	2.3	13	3.0	8	4.2	3	1.5	11	2.8
4	6	2.8	5	2.3	11	2.6	6	3.2	10	5.0	16	4.1
5	7	3.3	1	0.5	8	1.9	5	2.6	2	1.0	7	1.8
Total	214	100	214	100	428	100	190	100	199	100	389	100

D+ C+ D+ C− D− C+ see text p. 15.

Dyspnoea on exertion[a]		Asthmatic attacks[a]		Rhinitis[a]	
Birth cohort		Birth cohort		Birth cohort	
1/10/60–30/9/61	1/10/55–30/9/56	1/10/60–30/9/61	1/10/55–30/9/56	1/10/60–30/9/61	1/10/55–30/9/56
344 *(81.1)*	300 *(77.9)*	401 *(94.1)*	371 *(96.1)*	330 *(78.2)*	329 *(85.6)*
39 *(9.2)*	34 *(8.8)*	23 *(5.4)*	10 *(2.6)*	39 *(9.2)*	36 *(9.4)*
17 *(4.0)*	20 *(5.2)*	1 *(0.2)*	1 *(0.2)*	23 *(5.4)*	8 *(2.0)*
10 *(2.4)*	13 *(3.4)*	0	1 *(0.2)*	16 *(3.8)*	5 *(1.3)*
10 *(2.3)*	13 *(3.3)*	1 *(0.2)*	2 *(0.4)*	6 *(1.4)*	4 *(1.0)*
4 *(0.9)*	5 *(1.3)*	0	1 *(0.2)*	8 *(1.9)*	2 *(0.5)*
424	385	426	386	422	384

[a] Criteria see Table 9*a*.

Table 11 *Number and percentage of children according to symptoms and previous history (population A)*

Positive answer on question[a]		Cough >3 months a year				Cough >3 consecutive months a year				Cough 2 consecutive months a year				Cough 1 consecutive months a year			
		1–5×		0×		1–5×		0		1–4×		0×		1–4		0×	
		N	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%
36*h* ('68)	178	62	48.8	116	16.7	37	56.1	141	18.8	14	40.0	164	21.0	44	44.9	134	18.7
36*i* ('68)	308	103	81.1	205	29.8	58	87.8	250	33.4	23	65.7	285	36.5	56	57.1	252	35.1
36*j* ('68)	83	21	16.5	62	9.0	11	16.7	72	9.6	5	14.2	78	10.0	20	20.4	63	8.8
19 ('68)	206	65	51.2	141	20.5	38	57.6	168	22.4	17	48.6	189	24.2	39	39.8	167	23.3
12 ('69)	138	61	48.0	77	11.2	37	56.1	101	13.5	14	40.0	124	15.9	34	34.7	104	14.5
21 ('69)	115	47	37.0	68	9.9	33	50.0	82	10.9	10	28.6	105	13.5	27	27.6	88	12.3
28 ('69)	27	14	11.0	13	1.9	8	12.1	19	2.5	3	8.6	24	3.1	8	8.2	19	2.6
30 ('69)	22	11	1.6	7	10.6	15	2.0	3	8.6	19	2.4	6	6.1	16	2.2	16	2.2
Total number	815	127		688		66		749		35		780		98		217	

36*h* (1968) Did your child ever have periods of asthma or bronchitis?
36*i* (1968) Did your child ever have periods of cough?
36*j* (1968) Did your child ever have pneumonia?
19 (1968) Did your child ever wheeze?
12 (1969) Did your child ever have periods of cough for as much as 3 consecutive months in the previous years?
21 (1969) Has your child ever been troubled by shortness of breath when playing outdoors or walking up a staircase in the previous years?
28 (1969) When resting did your child ever have attacks with shortness of breath in winter in the previous years?
30 (1969) When resting did your child ever have attacks with shortness of breath in summer in the previous years?

Dyspnoea on exertion				Asthmatic attacks				Rhinitis				D+C+ D+C− D−C+			
1 5		0×		1–5		0		1 5		0		1 5		0	
N	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%	*N*	%
84	51.2	194	14.4	36	87.8	142	18.3	62	42.2	116	17 4	101	51.0	77	12.5
111	67 7	197	30.2	35	85.3	273	35.3	97	66.0	211	31.6	135	68.2	173	28.0
35	21.3	48	7.3	11	26.8	72	9.3	21	14.3	62	9.3	38	19.2	45	7.3
87	53.0	119	18.3	35	85.3	1 1	22.1	64	43.5	142	21.2	103	52.0	103	16.7
73	44.5	65	10.0	28	68.3	110	14.2	43	32.7	90	13.5	87	43.9	51	8.3
81	49.3	34	5.2	28	68.3	87	11.2	53	36.1	62	9.3	91	45.9	24	3.9
18	11.0	99	1.4	18	43.9	9	1.2	10	6.8	17	2.5	25	12.6	2	0.3
14	8.5	8	1.2	13	31 7	9	1.2	9	6.1	13	1.9	20	10.1	2	0.3
164		651		41		774		147		668		198		617	

Table 12. *Pulmonary function values according to symptom and age (population A + B)*

Age (years)	Cough ≥ 3 months a year: N	Mean $\frac{FEV_1}{FEV\,(E)}$ %	Mean FEV %	Cough ≥ 3 consecutive months a year: N	Mean $\frac{FEV_1}{FEV_1(E)}$ %	Mean FEV %	Cough 2 consecutive months a year: N	Mean $\frac{FEV_1}{FEV\,(E)}$ %	Mean FEV %	Cough 1 consecutive month a year: N	Mean $\frac{FEV_1}{FEV_1(E)}$ %	Mean FEV %
6/7	0			0			0			0		
7/8	2	84	79	0			0			4	93	81
8/9	27	93	78	13	98	79	8	96	81	18	93	80
9/10	25	93	79	1	96	80	11	95	80	25	94	77
10/11	20	97	80	10	97	78	2	84	76	12	98	78
11/12	17	94	80	8	96	79	0			0		
12/13	16	94	79	9	93	78	4	100	85	14	97	75
13/14	14	99	78	5	95	75	2	116	84	22	99	80
14/15	15	106	79	5	101	77	6	107	80	18	113	81
15/16	18	98	73	9	101	73	2	98	79	10	104	76

Age (years)	Dyspnoea on exertion: N	Mean $\frac{FEV_1}{FEV_1(E)}$ %	Mean FEV_1 %	Asthmatic attacks: N	Mean $\frac{FEV_1}{FEV\,(E)}$ %	Mean FEV %	Rhinitis: N	Mean $\frac{FEV_1}{FEV_1(E)}$ %	Mean FEV %
6/7	0			0			0		
7/8	4	94	83	0			6	96	78
8/9	53	96	79	5	90	74	51	95	79
9/10	60	93	79	6	93	78	45	95	79
10/11	36	93	78	6	82	72	32	96	79
11/12	18	92	76	12	88	74	16	93	80
12/13	62	93	78	8	91	72	23	93	77
13/14	49	98	78	7	94	75	26	95	79
14/15	56	100	78	7	84	67	19	96	77
5	35	99	76	4	89	64	29	103	77

Age (years)	D+C+ D−C+ D+C−: N	Mean $\frac{FEV_1}{FEV\,(E)}$ %	Mean FEV %	D−C− (c and/or w and/or n+)[a]: N	Mean $\frac{FEV_1}{FEV_1(E)}$ %	Mean FEV %	D−C− (c−w−n−)[a]: N	Mean $\frac{FEV_1}{FEV_1(E)}$ %	Mean FEV %
6/7	0			0			0		
7/8	4	94	83	14	97	79	56	96	81
8/9	60	96	79	111	99	81	335	99	82
9/10	63	93	79	95	95	78	358	99	81
10/11	47	94	78	93	97	79	366	97	80
11/12	27	93	77	51	98	82	283	96	81
12/13	66	93	78	59	93	79	306	95	81
13/14	50	98	77	68	98	80	271	100	81
14/15	59	100	78	55	105	80	285	104	81
15/16	43	101	76	49	106	80	287	105	80

Criteria, see text p. 15

[a] $FEV_{1(E)}$ = estimated FEV of children from the same population without a present or past history of respiratory disease according to the formulas. *Boys*: $^{10}\log FEV_{1(E)} = -3.37740 + 2.63690\ ^{10}\log$ height (cm) cl. *Girls*: $^{10}\log FEV_{1(E)} = -4.25738 + 3.03284\ ^{10}\log$ height (cm) in cl.

Table 13 *Pulmonary function values according to symptoms and numbers of years with symptoms (population A + B)*

Both birth cohorts are taken together

Number of years	Cough >3 months a year: N	Mean FEV_1/FEV_1(E) %	Mean FEV %	Cough >3 consecutive months a year: N	Mean FEV_1/FEV_1(E) %	Mean FEV %	Cough 2 consecutive months a year: N	Mean FEV_1/FEV_1(E)	Mean FEV	Cough 1 month a year: N	Mean FEV_1/FEV_1(E) %	Mean FEV_1/VC %
0	756	99	81	831	99	81	866	99	80	786	99	80
1	95	97	80	56	97	78	41	96	79	108	98	80
2	36	93	77	18	92	76	3	95	77	12	95	80
3	15	92	77	0			1	93	70	3	94	79
4	3	89	76	1	99	78	0			1	92	81
5	2	90	74	1	*110*	73	0			0		

Number of years	Dyspnoea on exertion: N	Mean FEV_1/FEV (E)	Mean FEV %	Asthmatic attacks: N	Mean FEV_1/FEV_1(E) %	Mean FEV	Rhinitis: N	Mean FEV_1/FEV_1(E) %	Mean FEV
0	709	99	81	852	99	81	732	99	81
1	86	96	79	41	96	78	85	97	79
2	47	98	80	8	90	72	44	96	78
3	29	98	79	2	90	66	24	97	82
4	28	94	76	3	81	67	13	93	76
5	8	89	73	1	80	70	9	90	73

Number of years	D+C+ D−C+ D+C−: N	Mean FEV_1/FEV_1(E) %	Mean FEV	D−C− (C and/or N and/or W+)[a]: N	Mean FEV_1/FEV_1(E)	Mean FEV %	D−C− (C−N−W−)[a]: N	Mean FEV_1/FEV_1(E)	Mean FEV
0	671	100	81	489	99	81	86	95	78
1	103	95	79	210	99	80	86	96	79
2	56	97	79	104	97	79	89	96	79
3	34	97	80	55	98	79	110	99	81
4	31	96	77	40	95	80	204	100	81
5	13	89	73	9	98	80	332	100	81

Criteria, see text p. 15. For statistical evaluation see text p. 17

$FEV_{1(E)}$ = estimated FEV of children from the same population without a positive present and past history of respiratory symptoms, according to the formula's: *Boys:* $^{10}\log FEV_{1(E)} = -3.37740 + 2.63690$ ^{10}log height (cm) in cl. *Girls:* $^{10}\log FEV_{1(E)} = -4.25738 + 3.03284$ ^{10}log *height* (cm) *in cl.*

Table 14 *Number and percentage of children according to median value of histamine threshold, symptoms and number of years with symptoms (population A+B)*

Only children with at least 3 histamine threshold values have been listed. In parenthesis: in % of total number (*N*).

Number of years	Cough >3 months a year				Cough >3 consecutive months a year				Cough 2 consecutive months a year			
	N	<8	16	>32	*N*	<8	16	>32	*N*	<8	16	>3
0	711	14 (2.0)	69 (9.7)	628 (88.3)	785	19 (2.4)	77 (9.8)	689 (87.8)	814	24 (2.9)	84 (10.3)	706 (86.7)
1	93	6 (6.4)	10 (10.7)	77 (82.8)	55	3 (5.4)	10 (18.2)	42 (76.3)	40	1 (2.5)	4 (10.0)	35 (87.5)
2	36	4 (11.1)	7 (19.4)	25 (69.4)	16	3 (18.8)	1 (6.2)	12 (75.0)	3	0	0	3
3	13	1	0	12	0	0	0	0	1	0	0	1
4	3	0	2	1	1	0	0	1	0	0	0	0
5	2	0	0	2	1	0	0	1				

Number of years	Cough consec. 1 month a year				Dyspnoea on exertion				Asthmatic attacks			
	N	<8	16	>32	*N*	<8	16	>32	*N*	<8	16	>32
0	735	22 (3.0)	67 (9.1)	646 (87.9)	666	8 (1.2)	55 (8.2)	603 (90.5)	806	15 (1.9)	74 (9.2)	717 (88.9)
1	108	3 (2.8)	18 (16.7)	87 (80.5)	85	6 (7.0)	7 (8.2)	72 (84.7)	40	5 (12.5)	11 (27.5)	24 (60.0)
2	11	0	1	10	44	3 (6.8)	13 (29.5)	28 (63.6)	8	3	2	3
3	3	0	2	1	29	2 (6.9)	8 (27.6)	19 (65.5)	1	0	1	0
4	1	0	0	1	27	4 (14.8)	5 (18.5)	18 (66.7)	2	1	0	9
					7	2	0	5	1	1	0	0

Number of years	Rinitis				D+C+ D−C+ D+C−			
	N	<8	16	>32	*N*	<8	16	>32
0	686	13 (1.9)	60 (8.7)	613 (89.3)	628	8 (1.3)	46 (8.7)	574 (89.3)
1	82	5 (6.1)	9 (11.0)	68 (82.9)	103	5 (4.8)	13 (12.6)	85 (82.5)
2	45	3 (6.7)	9 (20.0)	33 (73.3)	52	2 (3.8)	15 (28.8)	35 (67.3)
3	23	1 (4.3)	5 (21.7)	17 (73.9)	34	3 (8.8)	6 (17.6)	25 (73.5)
4	13	1	2	10	29	2 (6.9)	8 (27.6)	19 (65.5)
5	9	2	3	4	12	5	0	7

Criteria, see text p. 15. For statistical analysis see text page 19

Table 15*a*. *Number of children according to birth cohort and skin test reactions in 1968, 69 and 1973 (population A + B)*

In parenthesis. of total number

Birth cohort 1/10, 60–30, 9, 61

1968 1969	1973 Negative	1973 Positive	Total
House dust			
Negative	182	30	212
Positive	5	24	29 (*12*)
Total	187	54 (*22*)	241
Grass pollen			
Negative	219	16	235
Positive	2	4	6 (*2*)
Total	221	20 (*8*)	241
Animal danders			
Negative	204	27	231
Positive	3	7	10 (*4*)
Total	207	34 (*14*)	241

Birth cohort 1/10, 55–30, 9 56

1968 1969	1973 Negative	1973 Positive	Total
House dust			
Neg.	93	28	121
Pos.	2	28	30 (*20*)
Total	95	56 (*37*)	151
Grass pollen			
Neg.	125	19	144
Pos.	1	6	7 (*5*)
Total	126	25 (*16*)	151
Animal danders			
Neg.	115	17	132
Pos.	1	18	19 (*12*)
Total	116	35 (*23*)	151

Table 15*b* *Number of children according to number of years with symptoms and skin test reaction in 1968/69 and 1973 (population A+B)*

In parenthesis, in % of total. For statistical analysis, see text p. 22.

Skin tests[a]	68/69	73	Cough > 3 months a year Number of years: 0	>1	Cough > 3 consec. months a year Number of years: 0	>1	Cough 2 consec. months a year Number of years: 0	>1
House dust	−	+	48 (83)	10	52 (90)	6	56 (96)	2
	+	+	40 (78)	11	44 (86)	7	49 (96)	2
Grasspollen	−	+	26 (76)	8	28 (82)	6	33 (97)	1
	+	+	6 (60)	4	8 (80)	2	9 (90)	1
Animal danders	−	+	34 (72)	9	38 (88)	5	42 (98)	1
	+	+	17 (68)	8	18 (72)	7	24 (96)	1
All skin tests	−	−	219 (83)	46	242 (91)	23	250 (94)	15

[a] Means, concentration of house dust 0.5 mg/ml or less, concentration of grass-pollen 1 000 NE or less, concentration of animal danders 0.25 mg/ml or less.

Table 16 *Chest X-rays according to symptom groups (population A+B)*

Symptom-groups[a]	Line shadows: Normal	Increased	Unknown	Total	Mottled shadowing: Not present	Present but not marked	Marked	Unknown	Total
D+C+	17	1	0	18	18	0	0	0	18
D+C−	93	0	0	93	92	0	1	0	93
D−C+	28	2	0	30	28	0	0	0	28
D−C−	1 022	4	6	1 032	1 020	5	0	6	1 031
Unknown	6	0	0	6	6	0	0	0	6
Total	1 166	7	6	1 179	1 164	5	1	6	1 176

[a] Criteria, see text p. 15

Cough 1 consecutive month a year Number of years		Dyspnoea on exertion Number of years		Asthmatic attacks Number of years		Rhinitis Number of years		D+C+ D−C+ D+C− Number of years		Total number
0	>1	0	>1	0	>1	0	>1	0	>1	
52 (90)	6	47 (81)	11	56 (96)	2	49 (84)	9	45 (77)	13	58
39 (76)	12	33 (65)	18	43 (84)	8	36 (71)	15	30 (59)	21	51
29 (85)	5	23 (68)	11	29 (85)	5	24 (71)	10	20 (59)	14	34
8 (80)	2	7 (70)	3	9 (90)	1	6 (60)	4	6 (60)	4	10
37 (86)	6	35 (81)	8	41 (95)	2	35 (81)	8	30 (70)	13	43
17 (68)	8	9 (36)	16	17 (68)	8	12 (48)	13	9 (36)	16	25
235 (88)	30	223 (84)	42	256 (97)	9	220 (83)	45	210 (79)	55	265

Table 26. *Relative risks[a] for respiratory symptoms in one or more of the five years*

	Cough >3 months >1 pos.	Cough >3 consec. months >1 pos.	Cough 2 consec. months >1 pos.	Cough 1 consec. month >1 pos.	Dyspnoea on exertion >1 pos.	Asthmatic attacks >1 pos.	Rhinitis >1 pos.	D+C+ D+C− D−C+ >1 pos.
36*h* ('68)[b]	3.5	4.2	2.7	3.1	3.6	20.0	2.7	3.8
36*i* ('68)[b]	6.7	9.5	3.5	2.3	3.6	11.0	3.1	3.7
36*j* ('68)[b]	1.8	1.6	1.5	2.2	2.3	3.3	1.5	2.1
19 ('68)[b]	3.2	3.6	2.7	1.9	3.2	17.0	2.2	3.1
12 ('68)[b]	4.4	6.8	3.3	2.8	4.1	10.0	2.3	4.0
21 ('69)[b]	3.7	5.8	2.3	2.3	5.8	12.0	3.5	5.3
28 ('69)[b]	3.7	4.3	2.8	2.7	3.5	22.3	2.2	4.2
30 ('69)[b]	3.3	4.6	3.5	2.3	3.4	14.6	2.4	4.1

[a] The relative risk is calculated as follows. q 36 h was answered positively by 178 children and negative by 637 children
62 out of the 178 (35%) had >1 years cough for 3 or more months
65 out of the 637 (10%) had >1 years cough for 3 or more months.
Relative risk of a child with asthmatic attacks or bronchitis to develop cough for 3 or more months in later life is 35/10 = 3.5.

[b] 36*h* (1968) Did your child ever have periods of asthma or bronchitis?
36*i* (1968) Did our child ever have periods of cough?
36*j* (1968) Did your child ever have pneumonia?
19 (1968) Did your child ever wheeze?
12 (1969) Did your child ever have periods of cough for as much as 3 consec. months in the previous years?
21 (1969) Has your child ever been troubled by shortness of breath when playing outdoors (running) or walking up a staircase in the previous years?
28 (1969) When resting, did your child ever have attacks with shortness of breath in winter (summer) in the pre-
30 vious years?
Criteria, see text p. 15.

List of Supplements to Acta Paediatrica Scandinavica

(A list of earlier supplements can be obtained from Almqvist & Wiksell Tryckeri AB, Uppsala, Sweden without charge.)

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ESPGAN Committee on Nutrition

GUIDELINES ON INFANT NUTRITION

I. Recommendations for the Composition of an Adapted Formula

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Industrially produced infant foods are widely used nowadays Such foods have to a great extent been developed on a national basis as have the recommendations for their use During recent years there has been inter national progress in research in certain areas of gastroenterology kidney physiology inter mediate metabolism and developmental bio-chemistry which has a bearing on the subject of infant nutrition In order to summarize the implications for infant feeding of this new knowledge the Committee has worked out the following guidelines It must be emphasized, however that research continues and that further knowledge may necessitate changes in these guidelines

Breast feeding is superior to any other feed ing system for infants and it is considered unnecessary to elaborate on this. These guidelines concern recommendations for the composition of a substitute for human milk to be used during the first part of infancy in cases where breast feeding is not possible or the supply of milk is insufficient.

For many nutrients data are not yet available for precise recommendations In such cases fairly wide ranges have been given based on an evaluation of the advantages and disadvantages of too low and too high intakes For ethical reasons certain data can never be obtained from healthy human infants. Conclusions must therefore be drawn from animal experiments from studies in premature infants and from studies on pathological situations in human beings with all the inherent weaknesses of such deductions.

No attempt is made to set guidelines for the feeding of low birth weight or sick infants Furthermore the guidelines do not consider in the problem of contamination with for ...stances which may be harmful to the h as pesticides DDT and similar radioactive substances (e g. Sr[90])

TERMINOLOGY

Infant

The term infant means a person not more than 1? months of age

Infant formula

The term infant formula should be used as a name for products designed for bottle feeding of infants Infant formula is a food for infants which is suitable as a complete or partial substitute for human milk in meeting the normal nutritional requirements of infants.

Names of infant formulae

The name of an infant formula should be based on the source of the protein in it (e g. cow s milk beef soya, etc)

Types of infant formulae

There are two types of infant formulae starting formulae and follow-up formulae.

(*a*) *Starting formula* The term starting formula (or complete infant formula) is used for a formula which after reconstitution according to the recommendations of the manufacturer is intended to cover by itself all the nutritional needs of the infant during the first 4–6 months of life although it may be used—in addition with other infant foods—up to 1 year of age Starting formulae can be divided into two groups. 1) the starting formula in general corresponding to Codex Alimentarius "infant formula" which is designed for the full-term infant during the whole of infancy 2) the adapted starting formula adapted especially to the newborn physiology and thus fulfilling certain more specified requirements as presented below However this formula too can be used later

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Codex Alimentarius means in this document the report of the ninth session of the Codex Committee on Foods for Special Dietary Uses, Bonn, 22–26 September 1975 Alinorm 76/26 A.

ACTA PÆDIATRICA SCANDINAVICA

SUPPLEMENT 262 1977

ESPGAN Committee on Nutrition

GUIDELINES ON INFANT NUTRITION

I Recommendations for the Composition of an Adapted Formula

STOCKHOLM

At the 7th Meeting of the European Society
for Paediatric Gastroenterology and Nutrition
(ESPGAN) in Verona, 1974

the Society decided to appoint a Committee to consider standards and regulations on nutrition in infancy and childhood. The Committee decided to consider recommended compositions of formulae and other foods for infants recommendations for parents and their advisers regarding infant feeding, health education with regard to infant feeding and suggestions for medical standards for marketing of infant foods This document, Recommendations for the Composition of an Adapted Formula was discussed thoroughly at the 9th meeting of the Society in Weimar 1976

Almqvist & Wiksell Uppsala 1977

Industrially produced infant foods are widely used nowadays. Such foods have to a great extent been developed on a national basis as have the recommendations for their use During recent years there has been international progress in research in certain areas of gastroenterology kidney physiology intermediate metabolism and developmental biochemistry which has a bearing on the subject of infant nutrition. In order to summarize the implications for infant feeding of this new knowledge the Committee has worked out the following guidelines. It must be emphasized however that research continues and that further knowledge may necessitate changes in these guidelines

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No attempt is made to set guidelines for the feeding of low birth weight or sick infants Furthermore the guidelines do not consider in detail the problem of contamination with foreign substances which may be harmful to the infant such as pesticides DDT and similar compounds, radioactive substances (e. g. Sr^{90}) etc

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on in infancy as mentioned above The term adapted is preferred to humanized

(*b*) *Follow-up formula* This term means a formula which forms a part of a mixed feeding scheme intended for use from 4–6 months of age This formula, which in our view may differ from ordinary cow s milk for example through variations in quality and in quantity of fatty-acids as well as in respect of vitamin- and mineral content, may vary from country to country depending on local feedings habits [1]

SCOPE FOR AN ADAPTED FORMULA

The composition is primarily designed for full term and large preterm infants (b w more than 2 500 g.)

The feeding of such a formula implies that the minimal requirement of essential nutrients will be covered. It may be tempting to endeavour to do this with a certain margin of safety For reasons to be discussed too large a margin of safety may in the case of certain nutrients lead to adverse effects

Recent studies have shown that several organ functions are not fully developed in the ly months of life This applies for example the capacity of the intestinal tract to digest and absorb certain nutrients and to the capacity of the kidney to excrete metabolites of nutrients taken in excess The nutritional status may also play an important part in biochemical changes occurring in the developing brain. There is wide individual variation in the rate of maturation of development of function (biological variation) and in this connection the needs of infants on the minus side of the normal range are of particular importance

The capacity of different organ functions can also be temporarily or permanently impaired by disease of the organ for example decreased renal concentrating capacity in urinary tract infection

If organ function is not yet fully developed and/or is impaired the tolerance for certain nutrients will be limited and a too ample supply may lead to homeostatic disturbances because the capacity of the organ function concerned in the handling of the nutrient is exceeded. The most common homeostatic disturbances are those of acid–base balance and of water balance the latter is in turn due to a disturbance of the salt balance Homeostatic disturbances will be more likely to occur in certain situations such as diarrhoea, fever and increased environmental temperature It may thus not be sufficient to see that the infant gets enough of a nutrient it may also be necessary to consider not giving too much. This is not a problem in breast feeding as the composition of human milk is adjusted to the capacity of the developing organs.

In summary the composition of an adapted formula for use in the immediate postnatal period should not only cover the essential nutritional needs of the baby but also be adapted to the limited tolerance for certain nutrients in this period of life Furthermore the composition should include a reasonable margin of safety for still further decreased tolerance in disease and for minor errors in the preparation (reconstitution) of the formula by the parents which are common in many countries.

GENERAL ASPECTS

An adapted formula should resemble human milk as far as is possible and should not contain starch or flour nor should it be acidified (this applies also to l-acid) or include other substances such as honey so-called "growth factors or thickening agents whose possible side effects in either the short or long-term have not been adequately defined.

The formula should be isotonic in order to minimize the shift of water between different

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It should be noted that the 27th World Health Assembly in a resolution on infant nutrition and breast feeding, has requested the Director-General to promote and further support acti ities related t the preparation and use of weaning foods based on local products (WHO 27/43 23 May 1974)

body compartments In particular excess of minerals must be avoided. Di- or oligosaccharides rather than monosaccharides should be the principal carbohydrate for providing energy without increasing the osmolality of the formula To provide sufficient energy without increasing the osmolality fat should contribute around 50% of the energy even when di- or oligosaccharides are used

COMPOSITION

(When reconstituted as instructed by the manufacturers)

Energy

Energy: 68 (64–72) kcal/100 ml

Note

1 kcal=4 184 kiloJoules (kJ) Conversion figures for available calories according to the recommendations of WHO/FAO are as follows 4 kcal/g for protein 9 kcal/g for fat and either 4.2 or 3 75 kcal/g for carbohydrate depending upon whether the carbohydrate is expressed as polysaccharides or as monosaccharides (48) (According to the report of a Joint FAO/WHO Committee the energy available to the body is the gross energy of the diet minus the losses in urine and faeces)

Comments

The recommendation for calorie density is based on the mean energy content of human milk because there is no other firm basis for such a recommendation It should be noted however that there are variations in the energy content of human milk between populations between individuals, and even in the same individual between different periods of lactation and between different periods of the same feed

Little is known about the regulation of the calorie intake of infants Studies by Fomon et al. (26) indicate the existence of an appetite regulating mechanism. Although a calorie related mechanism for appetite seems to operate from about 6 weeks of life infants fed formulae with high calorie density still have a higher total calorie intake than those receiving formulae with lower calorie density The existence of an appetite-control mechanism based on the changing composition of the milk during the feed has been suggested in breast fed babies (39) This may explain the lower incidence of obesity in breast-fed infants

Formulae with high energy content tend to have high osmolality this may increase the thirst of the infant and thus leads to over feeding.

Protein

Protein 1 8–2.8 g/100 kcal (1.2–1 9 g/100 ml)

Note

The chemical index of the protein should be at least 80% of that of human milk as given in the FAO report on amino acid composition of food (22) In formulas providing the minimum quantity of protein the quality should be 100% of this reference when the quality of the protein used is lower the minimum quantity should be proportionally higher to compensate for this. In any case the nutritional value of the protein should not be less than 85% of that of the value of casein as defined by Codex Alimentarius.

Comments

Minimum value The minimum protein requirement of the infant below 6 months of age is not known with certainty The factorial method cannot be applied at this age and too few data of nitrogen balance studies are available. Thus the values usually accepted as "optimum" derive from measurement of the spontaneous intake of healthy breast fed infants and to allow for biological variations the figures given are 2 S D above the mean. 2.4 g/kg between 0 and 3 months of age and 1 85 g/kg between 3 and 6 months of age (49) The recommendations of the Food and Nutrition Board of the National Research Council (FNB) and of WHO/FAO are derived from these figures (30 48)

Experimental feeding studies in infants aged 8–111 days using cow s milk (28) or isolated soya protein (27) as a source of protein showed that growth comparable to that in breast fed infants of the same age was achieved with a protein intake of 1 74 g/kg/day

It appears therefore that in the neonatal period the minimum nitrogen requirement is covered by protein supplies of about 2 g/kg/day (1 8 g/100 kcal) It is even possible that the protein (but not nitrogen) requirement is lower since FNB recommendations (30) are based on the assumption that the protein content of human milk is about 25% higher (1 1–1 2 g/100 ml based on nitrogen analysis) than it actually seems to be (0 9±0 15 based on amino acid analysis) because human milk contains a large percentage of non-protein nitrogen (40) The nutritional implication of this possibility has not yet been completely evaluated.

However whatever the final conclusion may be all these calculations are only of practical significance if the amino acid composition of the formula protein is identical (or almost) with that of human milk protein. This is the only protein completely utilizable by the immature newborn in the first weeks of life For other proteins the minimum requirement of one or several essential amino acids might not be covered at such a low intake and this could have consequences for growth and biochemical maturation. Other amino acids supplied in excess amounts can provoke a potentially harmful increase of blood urea, ammonia and certain amino acid levels, this may happen with formulae prepared from non-modified cow s milk proteins, the composition of which differs greatly from that of human milk protein (78 79) The difference is largely due to the high proportion of lactalbumin (whey protein) to casein in human milk (lactalbumin/casein ratio 1) compared to that of cow s milk (lactalbumin/casein ratio 18 82) Casein has a relatively high content of aromatic (phenylalanine and tyrosine) and branched chain (leucine valine isoleucine) amino acids and an extremely low cystine content thus the methionine/cystine ratio (7 74) is 2–3 times higher than in other animal proteins and about 10 times that in human milk (0 69) or whey proteins (0 7?) (40) However low protein formulas in which demineralised whey consisting mainly of lactalbumin has been added to cow s milk protein have an amino acid composition fairly close to that of human milk.

Maximum value The reasons for this recommendation are as follows

1 *Renal solute load* The renal concentration capacity to excrete nitrogenous substances—mainly urea—from dietary protein and minerals is not fully developed in early infancy (89 103) With certain assumptions the sum of these solutes requiring excretion in the urine (usually referred to as the renal solute load) can be estimated. Such an estimation is of course only approximate due i.a. to variations in the fraction of synthesized body tissue (averaging 0 9 mOsm of the potential solute load of the formula per g of weight gain) loss through skin and in the stools (extrarenal losses are approximately 4 mOsm/kg between birth and 4 months of age) A rough calculation of this load is however possible. each gram of protein added to a formula above the protein minimum requirement can be considered to yield 5 7 mOsm (108) An intake of protein as high as that of unmodified cow s milk (5 g/100 kcal) implies therefore by itself (i e independently of the usual higher mineral content of the formula) a potential threat to the water balance of the body if the renal concentration capacity is as low as 200 mOsm/l (mean −2 S D at 2 weeks of age) or even when this capacity is in the order of 500 mOsm/l (mean −2 S D at 3 months of age)

Naturally a concomitant increase in the mineral content of the formula adds to this threat. The risk of a deranged water balance

increases considerably in situations with increased extrarenal water losses (due to e.g. fever increased environmental temperature or diarrhoea) and with impaired renal concentration capacity (e.g. in urinary tract infections) and, furthermore if the formula (water) intake is low (below 150 ml/kg)

... *Acid–base homeostasis* One of the main contributors to the net acid input (NAI) to the kidneys is non-metabolizable acid derived from oxidation of sulphur-containing amino acids from protein. Variations in NAI must be matched by the buffering capacity of the kidneys—measured as renal net acid excretion (NAE)—to preserve normal acid–base balance

The buffering capacity of the kidneys is also not fully developed in early infancy It has been found that the NAE response to an induced acidosis is especially low in preterm infants during the first month and that there is a wide variation in this response (88) Even on a moderate intake of protein (3.3 g/kg/day corresponding to 2 ? % protein in the formula) the reserve capacity of these infants to excrete H^+ ions may therefore be rather small In agreement with this finding the frequency of so-called late metabolic acidosis (base excess below −8 0 mEq/l) was found to be related to the protein intake at an intake of cow s milk protein of 3.3 g/kg/day the frequency in pre term infants (mean birth weight . 180 g, mean gestational age 34 weeks) was found to be 25% In term infants on a protein intake of 5 7 g/kg/day metabolic acidosis was however infrequent (87).

3 *Metabolism of amino acids* The newborn infant has a limited capacity for metabolism of amino acids because many of the enzymes involved are relatively inactive at birth (77). Cystine for example which in the adult and older child is produced during the degradation of methionine cannot be synthesized for a variable period after birth because the enzyme cystathionase is inactive (33) and possibly too in some premature infants due to immaturity of the methionine-activating enzymes and of cystationine-synthase. Thus, in the neonate cystine is an essential amino acid (72) Cystine is also the precursor of taurine, an amino acid that probably has a major role in brain development (86)

Amino acids consumed in excess of the infant s capacity for anabolism and degradation accumulate in the body and lead to elevation of the plasma amino acid levels. This is particularly frequent in low birth-weight infants especially with protein intakes exceeding 4.5 g/kg/day (corresponding to a protein content of 3 g/100 ml) and an amino acid composition of the protein corresponding to that of cow s milk (lactoglobulin/casein 18 82) The amino acids most often affected are tyrosine phenylalanine, threonine valine, leucine isoleucine, methionine and glycine. Some infants may have high levels persisting for weeks or even months. Plasma amino acid patterns similar to that of breast-fed infants are obtained with protein intakes of ..5 g/kg/day (1.5 of protein/100 ml) and lactoglobulin/casein ratio corresponding to that of human milk (60 40) (8 13 78). Persistently high levels of methionine phenylalanine or tyrosine are occasionally found also in full term infants receiving very high protein intake (53). Even breast-fed infants may occasionally show transient elevations of amino acids in plasma (41) which may be regarded as normal during the phase of adaptation to extra-uterine life.

The clinical significance of these plasma amino acid elevations is uncertain. It may depend on the particular amino acid(s) involved the degree and duration of the elevation and the state of maturity of the infant. At birth the human brain is in a phase of rapid growth which lasts until the end of the second year of life (19) and a long-lasting biochemical insult at this critical phase may have a permanent effect on brain function. High concentrations of single amino acids inhibit uptake of other amino acids, protein synthesis, and myelinization of the rat brain. It postulated (20) that such a counts for the intellectual impai

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palmitic acid) (76) The better absorption of human milk fat than of cow s milk fat can thus be related at least in part to the differences in triglyceride structure since human milk TG contains 7% of stearic acid and has most of its palmitic acid in the internal position (75%) whereas cow s milk TG contains 10–13% of stearic acid and has palmitic acid randomly distributed to the three positions of the glycerol molecule (23 75 90)

Another important feature to be taken into account when comparing the fat absorption coefficients of human and cow s milk is their differing content of mineral elements and particularly of calcium, which is known for its tendency to form non-absorbable salts There is in fact a relationship between fat and calcium excretion in the stools (42 96 102) Calcium absorption increases as the content of stearic and palmitic acids in the ingested lipids decreases (4? 102) and fat absorption increases as the calcium concentration of the formula decreases the amount of long chain saturated fatty acids remaining constant (96)

An adapted formula for term infants has to allow an absorption of at least 85% of the ingested fat in full-term infants at 1 month of age even if fat contributes half of the calories of the formula. This goal can probably be achieved when stearic and palmitic acids randomized comprise less than 10% and 20% respectively in weight of the total acids of the triglyceride and/or a relatively great proportion of the palmitic acid is located in the internal position of the glycerol molecule (e g. through using lard partly as a source of fat) and if the calcium content of the formula is lower than 50 mg/100 ml or 75 mg/100 kcal.

Animal and more especially vegetable fats are heterogenous in composition. This applies to their triglyceride structure to the component fatty acids to the cholesterol content and to the fat-soluble vitamin content. The properties of the fat in an infant formula (absorbability influence on serum lipid pattern specific biological effects etc) depend therefore on the kind of vegetable and/or animal fats used as the sources of the fat. Thus it is not meaningful to refer to vegetable or animal fats as nutritional terms without specifying their origin including the chemical composition. There is no scientific basis for the statement that a complete replacement of animal by vegetable fat is preferable in the manufacture of an infant formula.

3 Linoleic acid requirements Clinical evidence of essential fatty acid (EFA) deficiency occurs in the human infant when linoleic acid accounts for less than 0 1% of total calorie intake. On the other hand skin manifestations of EFA deficiency do not appear when linoleic acid comprises about 1% of calorie intake For this reason it has been estimated that minimal requirements for normal infants are covered by an intake of this order (9)

Biochemical changes in the fatty acid composition of the phosphoglycerides in the red cell stroma, in the absence of clinical symptoms have been found after a period of 3 weeks in a group of premature infants fed a diet containing only 0 6% of total calorie intake as linoleic acid there was a decrease in the percentage of linoleic acid and an increase in that of oleic acid and 20 3ω9 acid with a consequent rise of the triene/tetraene ratio (9) Since the triene/tetraene ratio in heart muscle liver and serum of experimental animals has been demonstrated to correlate well with clinical symptoms of EFA deficiency the biochemical changes may be considered as subclinical manifestations of EFA deficiency In 1–3 month old babies receiving linoleic acid in amounts of 3.5% of total calories the percentage of fatty acids of the linoleic acid series and the percentage of the sum of all polyunsaturated fatty acids in plasma and red cell stroma phosphoglycerides was found to be below that in babies immediately after birth or in adults (65 66) In infants at birth the stores of linoleic acid in the subcutaneous adipose tissue are small and there is consequently a decrease in linoleic acid in plasma free fatty acids and triglycerides within hours of birth

and the development of biochemical evidence of linoleic acid deficiency in plasma phosphoglycerides within a week if linoleic acid is not supplied in the diet (64 68 94) *In the rat studied during pre and postnatal development minimal changes have been noted in ethanolamine phosphatidyl glycerol brain content with low dietary supplies of EFA (1)* It is difficult to state precisely the significance of all of these observations with respect to the minimal linoleic acid requirement of the human infant.

Nor are there any precise data to indicate the safe upper limit for linoleic acid intake No clinical manifestations were observed when premature infants were fed for 40 days on a formula containing 35% of total fat as linoleic acid blood levels of linoleic acid in these babies were twice as high and linoleic acid in subcutaneous tissue was 2½ times higher than in premature infants fed on breast milk (10) No undesirable clinical effects of very high intakes of EFA have been recorded in large groups of children fed during infancy with formulas containing vegetable oil with a high content of polyunsaturated fat (corn oil)

Human milk in most parts of the world contains between 7 and 12% of total fat as linoleic acid corresponding to 3–6% of the total calories This is the main reason why this level *has been proposed as an advisable intake It is* recognised that the reasons for regarding the concentration in human milk as optimal are not strong as the level is dependent on the mother s intake of polyunsaturated fat. However such biochemical evidence as exists is in agreement with the recommendation

4 Dietary fat and serum cholesterol During recent years the relationship between the diet of the infant especially its fat component and the serum cholesterol level with its possible consequence for the development of atherosclerosis has been the subject of growing interest Thus in order to lower the serum cholesterol level various modifications of the fatty acid composition have been proposed in addition to a reduction in the cholesterol intake One such modification is a reduction of lauric and myristic acids to very low values as these fatty acids have been shown to be *strongly atherogenic in animal studies (56 105)* The same fatty acids have also been shown to be most potent in raising the serum cholesterol level in the human being (6 43) Another possible modification is an increase of linoleic acid at least to the same values as is found in the human milk of mothers whose diet is rich in polyunsaturated fat (i e to 6% of total calories) Together these two changes will have a slight to moderate effect on depressing the serum cholesterol level (37) No harm is known to occur from such a moderate dietary alteration and it is conceivable that some benefits may result (2)

It is well-known that breast fed infants have higher serum cholesterol levels than those found in infants fed on any infant formula This may be due in part to the high cholesterol content of breast milk the cholesterol concentration in breast milk is 30–40 mg/100 ml compared with 10–15 mg/100 ml in cow s milk and 1 to 3 mg/100 ml in most industrially produced infant formulae in which butterfat has been replaced in part or wholly by vegetable fats (70 107) No advantages of a high serum cholesterol level have been demonstrated Various studies have shown that the brain *can synthesize its own requirement of cho*lesterol and so probably can also other organs requiring cholesterol for their function (34) Recent work suggests that a high serum *cholesterol level in early life is not a pre* requisite for the development of adequate cholesterol homeostasis in the human being (3?) Nevertheless at the present state of knowledge *there does not seem to be suffi*cient reason to recommend any one feeding system for all infants on the basis of the serum cholesterol level

Carbohydrate

Carbohydrate 8–12 g/100 kcal (5 4–8 ? g/ *100 ml)*

Specific recommendations of carbohydrate composition

Lactose should constitute all or most of the total carbohydrate. The remainder should preferably be glucose and/or dextrin-maltose

Comments

The content of carbohydrate is around 7 g/100 ml in human milk 90% being lactose and the remainder oligosaccharides the role of which is not yet well understood Human milk does not contain fructose or sucrose

Lactose is hydrolysed mainly by the brush border lactase and is absorbed as glucose and galactose. Although lactase activity is almost completely mature soon after birth (7 47) a certain part of the lactose escapes and is fermented by colonic bacteria into lactic acid and low molecular weight fatty acids Therefore lactose is an important factor contributing to the low pH of the stools of breast-fed infants, which together with the low buffering capacity due to the low protein and low phosphate content of human milk is considered to be partly responsible for suppressing the growth of *E. coli* in the intestine of breast fed infants (16 104) The latter effect is influenced by the rate of mutarotation from beta-lactose to alfa-lactose which is split more rapidly In human milk mutarotation proceeds slowly thus providing more lactose in the lower gut (38)

Since it is not feasible as yet to reproduce the carbohydrate composition of human milk, a content of lactose as high as 7–8 g/100 ml seems justified even if it has been reported that such a load can induce systemic acidosis in young infants especially in prematures (31 54)

Lactose has the lowest degree of sweetness in comparison with other mono- or disaccharides offered to infants (25) There is no argument to justify the addition of sucrose whose role in the pathogenesis of dental caries is well established and discussed in the development of obesity and atherosclerosis.

Conclusive data on the relation of various carbohydrates in infant formulas and insulin secretion in prematures and young infants are not yet available.

Sodium Potassium and Chloride

The sodium content should not be less than that of human milk but should probably not exceed 1 76 mEq/100 kcal (12 mEq/l) The sum of sodium chloride and potassium should not exceed 50 mEq/l

Comments

The minimum salt requirement for the infant actually exceeds that of the adult 1–2 mEq of sodium per day is required for growth (0.33 mEq/kg during the first 20 weeks of life) skin and gastrointestinal losses are estimated to be 2 mEq under normal conditions (3 98) Thus 6–8 mEq of sodium per day comparable to that provided by human milk (1 mEq/100 kcal) seems adequate (25) and it could be dangerous to go below this value especially in preterm infants who may have a transiently reduced ability to retain sodium (5)

On the other hand newborns and very young infants have a reduced capacity to excrete excess salt. This is due not only to their lower glomerular filtration rate but also to a specific inability of the tubules to reject sodium selectively following a load of 1% saline the sodium elimination rate is about 1.5 mEq/hour/1 73 m^2 (range 0.3 to 3 mEq/hour/1 73 m^2) during the first 2 weeks of life instead of 6–10 mEq for older children with comparable low filtration rate secondary to renal disease (4) However the tolerance for salt is probably rather large although less than in adults, provided that the access of water is not limited Intakes of 100 mEq of sodium per day (10 mEq/100 kcal) without adverse effects have been observed (73) and the maximum tolerance of infants has been indirectly estimated to be 12 mEq/kg (4) There are convincing studies however showing in rats with genetic predisposition that an excessive salt intake in early life will result in hypertension later higher intakes (10–30 mEq/100 kcal) can even induce hypertension in non-

selected laboratory rats and some epidemiological observations suggest a relation between salt ingestion and hypertension in human beings (3) Furthermore even if the renal ability to excrete sodium is considerable in infancy with the limited water supply provided by bottle feeding, the renal concentration capacity becomes the limiting factor for the excretion of sodium and minerals in general Each mEq of Na^+ K^+ Cl^- and phosphorus excreted in the urine contributes about one mOsm to the renal solute load (108)

Thus in order to avoid a threat to the water balance including the risk of hypertonic dehydration and to minimize the risk of developing hypertension in adult life the mineral content of adapted formulae must be kept far below that of ordinary cow's milk Ideally this concentration should be that of mature human milk. It is not possible however to achieve this goal without demineralization. This process has been said to incur the hypothetical risk that certain, if as yet unidentified, nutrients might be removed (74) No undesirable clinical effects have however been recorded in infants fed demineralized formulae used for several years in many countries. Demineralization adds considerable costs to the manufacturing of the formula product It would therefore seem reasonable to choose as upper limit for sodium 12 mEq/l (1 76 mEq/100 kcal) and 50 mEq/l for the sum of Na^+ K^+ and Cl^- values which can be reached simply by dilution of cow's milk to a protein content according to the limits recommended above [1] This will ensure a sufficient margin of safety for the water economy of the body

Calcium and Phosphorus

Calcium minimum 60 mg/100 kcal (40 mg/100 ml)

Phosphorus minimum 30 mg/100 kcal (20 mg/100 ml) and maximum 50 mg/100 kcal (35 mg/100 ml)

Ca/P ratio not less than 1.2 and not more than 2.0

Comments

About 99% of the body calcium is retained in the skeleton (Ca/P ratio in bone minerals is 2.2) The calcium economy of the body is mainly regulated by the absorption urinary excretion is of less importance Absorption under the influence of vitamin D is adapted to need at higher intakes a relatively lower percentage is absorbed and vice versa. The formation of insoluble calcium compounds inhibits absorption. Excess phosphorus acts in this way and a high intake of fat especially fats which are badly absorbed has a similar effect

About 75% of body phosphorus is located in the skeleton the rest being in the soft tissues (the N/P ratio in soft tissues is 15) Absorption of phosphorus is partly regulated by calcium absorption impaired calcium absorption results in impaired phosphorus absorption due to the formation of insoluble calcium–phosphorus complexes

In breast fed infants calcium absorption amounts to about 75% of intake and results in a calcium retention of about 200 mg/day On the other hand formula-fed infants have a lower calcium absorption with values which may be as low as 20% The tendency to low calcium absorption is most marked during the first week of life particularly in premature infants and then improves gradually (11 12) Adequate retention is nevertheless obtained with a higher calcium intake than that accomplished through breast feeding and this is the main reason for the higher calcium content in infant formulae as compared with human milk (on average 30 mg/100 ml) (82)

Infants fed formulae with a higher content of phosphorus than in human milk (15 mg/100 ml) excrete a large part of this phosphorus in the urine Because the renal clearance capac

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[1] In cow's milk with protein content of 3 3 g/100 ml the sum of Na K and Cl 89 mEq/l (13 1 mEq/100 kcal). If cow milk is diluted to protein content of 1 9 g/100 ml (maximum value recommended in these guidelines) (corresponds to 2.8 g/100 kcal) the sum of the three ions will be 51 mEq/l (7.5 mEq/100 kcal)

ity of the newborn infant is not fully developed an upper limit for the phosphorus content and a lower limit for the Ca/P ratio has been set in order to minimize the tendency to hyperphosphatemia and hypocalcemia. Too high an intake of phosphorus will also add to the renal solute load (108)

Magnesium

Magnesium Minimum value 6 mg/100 kcal (4 mg/100 ml) (according to Codex Alimentarius)

Iron

Iron 0 1–0 2 mg/100 kcal (0 07–0 14 mg/100 ml) (formulae without iron supplementation)
Not less than 1 mg/100 kcal (0 7/100 ml) (formulae with iron supplementation)

Note

Formulae containing not less than 1 mg of iron/100 kcal shall be labelled "Infant formula with iron" (according to Codex Alimentarius)

Comments

Human milk and cow s milk have as the milk of nearly all mammals a low iron content comprising between 0 03 and 0 06 mg/100 ml (mean 0 05 mg/100 ml or 0 07 mg/100 kcal). Colostrum has a level 3 to 5 times higher but after the initial fall there seems little evidence of a significant decline through the rest of the lactation period (91)

Both breast feeding and formula feeding seem adequate to cover the needs of healthy full-term infants during the first 6–8 weeks of life as the iron of the red cell mass, which represents approximately two-thirds of the total iron content at birth [1] decreases by at least 50 mg during this period A small amount of the liberated iron (about 10 mg) is used for the synthesis of myoglobin but the largest part enters iron stores (84). Thus, up to this age iron requirements essentially consists of compensation for obligatory losses (from the gastrointestinal tract primarily in the form of desquamated epithelial cells from the skin and in the urine) which are estimated to be 0 ? to 0.3 mg/day Therefore there is no real justification for fortification of infant formulae with iron before the third month of life. Furthermore iron supplementation does not prevent the "physiological" fall of the red cell mass which is related to the shorter half-life of foetal red cells rather than to iron deficiency (69) full-term infants fed from birth on formulae with an iron content of 1 25 mg/100 ml do not have a higher serum iron concentration nor a significantly lower total iron-binding capacity (TIBC) at 2 months of age than those receiving formulae "without iron" (51 67)

From the third month onwards however the quantities supplied by milk (0 4 to 0 5 mg a day) are too low to cover the infant s needs even if the iron were completely absorbed which is not the case since only about 10% (or at most 30%) of the ingested iron is absorbed (91) The increase in the blood volume and the incorporation of iron in myoglobin correspond to an enlargement of the haem compartment of more than 100 mg between 2 and 6 months of age therefore taking into account the obligatory losses there is a requirement of absorbed iron of about 1 mg/day Nevertheless iron can usually be incorporated normally into haemoglobin by the majority of healthy full-term infants at the expense of their iron stores (hemosiderin and ferritin) but most will have a reduction of serum iron concentration and an increase in TIBC which bear witness to the depletion of body iron.

Infants born with small iron stores (for example preterm infants) (36) or in whom the intestinal blood losses are greater than average (106) cannot maintain their haemoglobin levels within the normal limits with the commonly used foods unless the milk is fortified with

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[1] The iron content of the full-sized infant at term is about 50 mg at birth and the part contained in the haemoglobin is estimated at 150 mg by the Cr^{51} technique (84) the same result is obtained assuming a blood volume of 70 ml/kg haemoglobin level of 18.5 g/100 ml and an iron concentration of 0.34% (.3).

iron Such fortification is therefore recommended (81)

Unfortunately estimates of the requirement for absorbed iron are of limited value in establishing recommendations for daily intakes of iron owing to the large variations in its absorption due to many factors such as the size of the iron stores etc (25) Thus 10 mg/day will be necessary if 10% of dietary iron is absorbed but only 7 mg will be required if the absorption is 15% Most calculations of iron requirements are in fact in good agreement with the experimental findings (62) which show that in infants between the ages of 3 and 12 months the addition of 5 mg of iron to an otherwise iron-deficient diet (consisting largely of milk) raised the haemoglobin concentration even in the normal infant. A concentration of iron in infant formulae equal to or greater than, 1 mg/100 kcal would therefore seem justified from the third month onwards

Finally it must be pointed out that recent reports have shown that free iron in infant formulae (i e an iron content exceeding the binding capacity of lactoferrin) will promote the growth of *E. coli* and thus might increase the susceptibility to infection of infants fed such formulae (14 15 21 55 59 93) The clinical relevance of these studies is unknown, it has not been shown that infants fed formulae fortified with iron have an increased frequency of gastroenteritis On the other hand studies on the prevention of infections through iron fortification (and thereby prevention of anemia) are also difficult to evaluate. It is doubtful if even for infants living in tropical countries under suboptimal hygienic conditions iron fortification of formulae will have any additional effect on bacterial growth that is of clinical significance For infants fed formulae prepared and stored under adequate conditions such an effect is unlikely and remains to be shown.

Zinc

Zinc Minimum value 0 3 mg/100 kcal (0.. mg/100 ml)

Comments

Zinc concentrations in the body vary relatively little throughout life values of ?0 mg/kg of fat-free body mass have been found in foetuses and full-term newborns whereas adults contain approximately 30 mg/kg (100) Only a small fraction of zinc—mostly bound to various enzymes—is stored in the liver which thus cannot be considered as an important storage organ as it is for copper and iron

Since infants roughly double their lean body mass in the first 6 months of life their total zinc content is also doubled during this period—provided the zinc concentration remains the same (80) The daily increase in zinc is thus about 350 μg (60 mg in 6 months) and the requirement can be estimated between 1 ? and 1 8 mg/day taking account of the fact that only 20–30% of ingested zinc is usually absorbed (80)

Thus human milk with an average zinc concentration of 0 15 to 0.20 mg/100 ml (71) provides a sufficient quantity and signs of zinc deficiency have never been recorded in breast-fed infants In consideration of the inhibition of zinc absorption by copper and also possibly by calcium and phosphorus (91) it is advisable for infant formulae (which have a higher mineral content than human milk and in which it is recommended to add copper) to have a zinc content at least in the lower range of cow s milk (0 20–0 65 mg/100 kcal) This explains the recommendation of 0.3 mg/100 kcal

Copper

Copper Minimum value 30 μg/100 kcal (20 μg/100 ml)

Comments

The milk of almost all animal species has a relatively low copper content (as is also the case for iron) (91) This is particularly true of cow's milk, the copper content of which varies (according to the nutritional supplies and the

stage of lactation) between 2 and 30 μg/100 ml with average values around 10 μg/100 ml. Human milk has a higher content of around 30 μg/100 ml for mature milk (71) but even breast fed infants often have a negative copper balance during the first weeks of life (17)

Such a negative balance however is usually of no clinical significance for full term infants since the liver at birth contains surprisingly large amounts of copper Its concentration is more than 10 times higher than in adult liver and the copper stored in the liver of the full-term infant as easily available complexes represents more than half the copper in the whole body (99)

For this reason it appears that the copper content of human milk, even though apparently low represents the ideal for full-term infants during the first months of life. An interaction between copper and zinc has been reported. An excess of zinc depresses the absorption of copper and the zinc/copper ratio is considerably higher in cow's milk than in human milk (91 98) This is the reason why according to Codex Alimentarius the recommended minimum copper concentration in formulae for full-term infants is 60 μg/100 kcal (corresponding to 40 μg/100 ml) a value reached at present in very few dried milk preparations sold in Europe (101) However for technical reasons (i.e. potential oxidation of the fatty acids through copper supplementation) we suggest a minimum copper concentration of 30 μg/100 kcal which takes into account the variations in the composition of human milk. It should be noted that clinical signs of copper and zinc deficiency have never been observed when feeding infants with non-copper and non-zinc enriched formulae based on cow s milk—except in special disorders and in malnutrition.

Other T ace Minerals

Available data are insufficient regarding other trace minerals The values recommended below are those given by Codex Alimentarius and these are in agreement with the values found in human milk

Iodine:
minimum alue: 5 μg/100 kcal (3 4 μg/100 ml)
maximum alue: non-specified

Manganese:
minimum alue: 5 μg/100 kcal (3.4 μg/100 ml)
maximum alue: non-specified

Vitamins

Vitamin requirements have been discussed very thoroughly in Codex Alimentarius and the Committee has found no reason to deviate from the values given by Codex Alimentarius It should be noted that in some countries the requirements for some vitamins are covered partly through enrichment of the formula and partly through supplementation with vitamin preparations.

The standards of Codex Alimentarius for vitamins are as follows.

	Amounts/100 kcal	
	Minimum	Maximum
Vitamin A	250 I U 75 μg expressed as retinol	900 I U 150 μg expressed as retinol
Vitamin D	40 I U	80 I U
Ascorbic acid	8 mg	None specified
Thiamine	40 μg	None specified
Riboflavin	60 μg	None specified
Nicotinamide	250 μg	None specified
Vitamin B_6	35 μg	None specified
Folic acid	4 μg	None specified
Pantothenic acid	300 μg	None specified
Vitamin B_{12}	0 15 μg	None specified
Vitamin K	4 μg	None specified
Biotin	1.5 μg	None specified
Vitamin E (α-tocopherol compounds)	0.7 I.U./g linoleic acid, but in no case less than 0.7 I U./100 available calories	

Formulae with protein content higher than 1.8 g protein/100 kcal should contain minimum of 15 μg vitamin B_6 per gramme of protein.

FOOD ADDITIVES FOR TECHNOLOGICAL PURPOSE AND OTHER TECHNOLOGICAL ASPECTS[1]

Thickening Agents

Besides their supposed effect on the infant s feeling of satiety thickening agents are some times used to increase and prolong the stability of fluid formulae If liquid protein fractions are used thickening agents become superfluous as stabilizers although prolonged stability can still be achieved when they are added Although Guar Gum Carrageenan modified starches and Locust Bean Gum are allowed by the Codex Alimentarius it is doubtful that there is any necessity to use these compounds in liquid formulae except possibly in formulae used for specific therapeutic purposes

So far our knowledge about the toxicological effects of thickening agents is incomplete There is a possibility in young infants of absorption by pinocytosis or by persorption with potentially dangerous consequences (95) There are insufficient data on the administration of thickening agents to animals to allow of conclusions with respect to infants (58) Thickening agents for technological purposes should therefore not be included in adapted formulae for infants younger than 4 months

Packing Material

Plastic materials have been increasingly widely introduced as packing materials for fluid formulae When plastic materials are so used one should beware of the deleterious effects of certain materials For example polyvinylchloride has proved to be strongly mutagenic and teratogenic in animals There is also a possibility that certain plastic hardeners such as di 2-ethylhexyl phthalate (DEHP) might be the injurious agent in causing infantile haemorrhagic enterocolitis (45 46)

Vitamin C in liquid products packed in certain plastic materials cannot be preserved and hence the content cannot be reliably declared When such products are used as the main food even over short periods of time vitamin C supplementation should be recommended on the label

[1] In regard to food addit es for technological purposes other than thickening agent the Committee agrees with the regulation stated by Codex Alimentarius The same applies to contaminant and pesticides

Heat Processing

Technological processing by heat always leads to varying degrees of protein damage especially through loss of lysine the epsilon-amino group of which reacts with certain sugars leading to Maillard reaction products so-called "browning products (44) Neither nitrogen determination nor amino acid analysis following acid hydrolysis alone can indicate lysine losses since acid hydrolysis liberates amino acids which have already been fixed in browning products The nutritional value of the protein should therefore be controlled (60) and fulfil the requirements of Codex Alimentarius

ESPGAN Committee on Nutrition.

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Congenital Dislocation of the Hip Joint

Clinical Studies with Special Reference to the Pathogenesis

By KAREL BJØRN CYVIN

ALMQVIST & WIKSELL PERIODICAL COMPANY STOCKHOLM

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CONGENITAL DISLOCATION OF THE HIP JOINT

Clinical Studies with Special Reference to the Pathogenesis

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KAREL BJØRN CYVIN

TRONDHEIM 1977

CONTENTS

Almqvist & Wiksell Uppsala 1977

To my children
Tarjei, Øylov and Jardar

TERMINOLOGY

In the present investigation *congenital dislocation of the hip joint (CDH)* covers the following terms

1 *Instability of the hip joint* or *unstable hips* denotes the readiness for dislocation in the newborn, diagnosed by the Ortolani's abduction manoeuvre and the subluxation provocation test. The terms are used synonymously with *preluxation*

2 *Neonatal CDH* or *early-diagnosis CDH* is used when the hip disorder was diagnosed in the first month of life *Late-diagnosis CDH* denotes detection after 1 month of age

3 *Dysplasia* of the hip denotes following changes observed on the roentgen examination. sloping acetabular roof indistinctly marked lateral margin small epiphysis of the femoral head and increased anteversion of the femoral neck

4 *Subluxation* or *dislocation* is used when the femoral head shows greater or lesser degree of displacement without complete loss of contact with the acetabulum.

5 *Luxation* denotes that the femoral head has completely lost contact with the acetabulum

INTRODUCTION

Congenital dislocation of the hip (CDH) represents one of the most important congenital abnormalities of the musculo-skeletal system. During the last decades both clinical and experimental studies have brought forward considerable information on the epidemiology, symptomatology and therapeutical results in CDH. Simultaneously there has been an important progress in the understanding of the etiology and pathogenesis of the disorder. Many problems, however, still remain unresolved, and several theories regarding the pathogenesis of CDH are not completely documented.

The aims of the present publication are as follows:

1) to describe the prenatal and perinatal characteristics of infants with unstable hips at birth (part I)

2) to give an evaluation of the role of breech presentation in infants with unstable hips at birth (part II)

3) to report results of investigations on the seasonal variation of birth dates of infants with unstable hips at birth (part III)

4) to present an analysis of infants with stable hips at birth and late-diagnosis CDH (the so-called "missed cases" of CDH)

I PRENATAL AND PERINATAL CHARACTERISTICS OF CHILDREN WITH UNSTABLE HIPS AT BIRTH

Despite numerous investigations on instability of the hip joint in the newborn the true nature of the abnormality is still obscure. It is agreed that the following conditions have some relation to unstable hips a genetic predisposition birth order of the child breech presentation and possibly maternal hormones and seasonal influences (3 12 15 46 50 59 67 70 85)

The present investigation was an attempt to find possible additional factors of importance in the pathogenesis of unstable hips by a detailed analysis of the prenatal and perinatal condition of the children affected

MATERIAL AND METHODS

From 1.5 1969 to 31 12.1974 19 864 children (10 240 boys and 9 624 girls) were born in the two maternity units in Trondheim (E. C Dahls ftelse and the Obstetrical Department of the ional Hospital Most of the mothers came m the city of Trondheim and the remainder from neighbouring communities

The newborns were examined at least twice the first examination on the first or second day and the second generally four to six days after birth About 15 000 of the children were examined by the author and the rest by one of the trained consultants of the Pediatric Clinic The hips were examined according to Palméns and Barlows modification of the Ortolani test (8 40)

During the period 1 5 1969–31 12 1974 instability of the hip joint w found in 378 children group A) Table I 1 shows the annual frequency and the sex distribution of the affected children

The control group of children (group B) consisted of 378 subjects of the same sex and born chronologically next to the children with unstable hips

Information regarding the prenatal and perinatal condition of the children was based on Hospital Records. The following data were recorded

Family history of abnormalities of the hip joint and other malformations.

The age of the mother parity and previous abortions or stillbirths

All signs of deviations from the normal course of the pregnancy such as proteinuria elevated blood pressure signs of infection diabetes Rhesus immunisation administration of drugs X-ray examinations or therapy and studies of the placental function

Estimated duration of pregnancy according to the last menstrual date

The course of delivery including the type of presentation special procedures (oxytocin induction rupture of membranes forceps or vacuum extraction and caesarian section) and the following complications. bleeding pathological foetal heart beats meconium stained liquor duration of delivery exceeding 24 hours and efflux of liquor more than 12 hours before delivery

The weight of the placenta and any macroscopically pathological appearances, especially infarcts and calcifications

The birth weight birth length head circumference and Apgar score of the child and pathological findings such as signs of dysmaturity hypotonia irritability jaundice and malformations.

Date of examination and name of the examiner location degree and duration of the instability of the hip and treatment instituted

The collected data were processed in a UNIVAC 1108 at the Computing Centre of the University of Trondheim. The mean values for group A and group B were computed Differences of means were tested by the t test and

Table I 1 *The frequency of newborns with unstable hips in Trondheim from 1.5 1969 to 31 12 1974*

	No. of children with unstable hips			No of liveborns			Frequency (per thousand liveborns)		
Year	Boys	Girls	Total	Boys	Girls	Total	Boys	Girls	Total
1969	5	37	42	999	927	1 918	8.50	39.90	21.90
1970	19	62	81	1 726	1 638	3 364	11 01	39.85	4.08
1971	14	51	65	1 889	1 834	3 723	7 41	27.81	17 46
1972	28	60	88	1 918	1 750	3 668	14.60	34.29	23.99
1973	16	39	55	1 946	1 732	3 678	8.22	22.52	14.95
1974	11	36	47	1 770	1 743	3 513	6.21	20.65	13.38
Total	93	285	378	10 240	9 624	19 864	9.08	29.61	19.03

P values below 0 05 were regarded as statistically significant. When indicated regression curves and confidence limits were computed Correlation coefficient >0 75 was regarded as positive.

RESULTS

Table I.2 shows the frequency of hip joint abnormalities in the families of affected and non-affected children As can be seen cases of congenital dislocation of the hip (CDH) occurred in 39 1st degree members of families of the affected children and in 4 members of families of the non-affected children. The difference is statistically significant.

Table I.3 shows the frequency of other malformations in families of children of groups A and B The figures are too small for definite evaluations.

Table I 4 shows the mean age of the mothers in the two groups. There is no statistically significant difference between the ages in group A and group B

Table I.5 shows the frequency of previous abortions or stillbirths in the mothers of group A and group B There is no statistically significant difference between the two groups

From Table I.6 can be seen that first-born children occurred significantly more frequently in group A than in group B

Table I 7 shows the frequency of various symptoms and signs during pregnancy of mothers of children with stable and unstable hips. There is no statistically significant difference between the two groups

Table I.2. *Hip joint abnormalities in the families of children with unstable hips at birth (group A) and in the families of control newborns (group B)*

	Group A			Group B		
Relatives	CDH	Other hip abnormal	Sum	CDH	Other hip abnormal	Sum
Boys						
1st degree	9	1	10	1	0	1
Others	7	3	10	2	1	3
Total	16 (18 %)	4	20 (22.5 %)	3 (3.3 %)	1	4 (4 4 %)
Girls						
1st degree	30	1	31	3	0	3
Others	28	9	37	11	8	19
Total	58 (20.1 %)	10	68 (23.5 %)	14 (4.8 %)	8	22 (7 7 %)

Table I.3 *The occurrence of malformations in families of children with unstable hips at birth (group A) and in families of control newborns (group B)*

Relatives	Group A Boys	Group A Girls	Group A Total	Group B Boys	Group B Girls	Group B Total
1st degree	1	3	4		6	8
Others		1	3	1	1	2
Total	3	4	7	3	7	10

Table I.4 *The mean age of mothers of 377 children with unstable hips at birth (group A) and the mean age of 376 mothers of control newborns (group B)*

	Group A Boys	Group A Girls	Group A Total	Group B Boys	Group B Girls	Group B Total
No. of subjects	89	288	377	90	286	376
Mean age in years	25 01	25 92	25 70	25 51	4 74	4 93
S.D	4 42	5 44	5 [illegible]3	5 10	4.63	4 75

Table I 8 shows the frequency of toxaemia in mothers of the two groups of children There is no statistically significant difference between the two groups

From Table I 9 can be seen the occurrence of different infections in mothers of affected and unaffected children There is no statistically significant difference between the two groups

The administration of drugs to mothers of children with unstable and stable hips is shown in Table I 10 Both diuretics and antibiotics were given more often to the mothers of children in group A than to the mothers of children in group B but the differences are statistically not significant

Table I 11 shows the birth presentation of ldren with unstable and stable hips at birth. e left occiput anterior presentation appeared significantly more frequently in group B than in group A whereas the breech presentation appeared more frequently in group A than in group B On the basis of A≠B-hypothesis there was statistically no significant difference between the occurrence of right occiput anterior presentation in the two groups but if A>B-hypothesis was adopted also the right occiput anterior presentation appeared significantly more often in group B than in group A.

Table I 12 shows the frequency of special procedures during the delivery of mothers of children with unstable and stable hips Both oxytocin induction forceps or vacuum extraction and caesarian section was instituted more often in mothers of affected children than of the unaffected The difference between the two groups was statistically significant

Table I 13 shows the indications for caesarian section in mothers of children with unstable hips It can be seen that in 11 cases (above 50 per cent) the main indication was mechanical disproportions.

Table I 14 shows the indications for caesarian section in mothers of children with stable hips Only in two cases was the section performed for mechanical reasons.

Table I.5 *Previous abortions in mothers of children with unstable hips at birth (group A) and in mothers of control newborns (group B)*

	No of abortion											
	0		1				3		4		Total	
	No		No		No	%	No	%	No	%	No.	
Group A	333	88		9	10	6		0 5	0	0 0	45	11 8
Group B	327	86		10	9	4	1	0 3	1	0.3	51	13 6

Table I 6. *The birth order of newborns with unstable hips (group A) and control newborns (group B)*

	Group A		Group B	
	No.	%	No.	%
First born	189	50.1	152	40.3
Second- or later born	188	49.9	225	59 7

Table I 15 shows the different complications of delivery for the two groups of children All the recorded complications appeared more frequently in group A than in group B

The mean gestational period of the affected and non-affected children is shown in Table I 16 The difference between group A and group B is statistically significant both for boys and for girls. Duration of pregnancy exceeding 294 days was recorded in 73 mothers of group A (45.9 per cent) and in 52 mothers of group B (32.7 per cent) Fig. I 1 illustrates the distribution curves for the values of groups A and B

From Table I 17 can be seen that there was no statistically significant difference between the mean duration of gestation in the first born babies compared with the second or later born babies

Table I 18 shows the mean birth weight of children with unstable and stable hips The difference between values of girls in the two groups is statistically significant. Fig. I.2 illustrates the distribution curves of the values.

Table I 19 shows the correlation of birth weight and the gestational period in children with unstable hips and Table I.20 shows the corresponding results in children with stable hips As can be seen there is no difference in the frequency of small for date or large for date» babies between the two groups The number of children born after a gestational period exceeding 41 weeks was significantly higher in group A than in group B but those children fell within the 10–90 percentiles for weight.

From Table I.21 can be seen that the mean birth weight of first-born children did not differ significantly from that of second or later born children.

Table I.22 gives the mean values of the birth length of children with unstable and stable hips The difference between the two groups is

Table I 7 *Various symptoms during the pregnancy of 378 mothers of children with unstable hips at birth (group A) and in 378 mothers of control newborns (group B)*

	Group A		Group B	
	No	%	No.	%
Emesis	11	.9	7	1 9
Early bleeding	10	2.6	10	2.6
Late bleeding	4	1 1	4	1 1
Bleeding, unspecified	0	0.0	1	0 3
Polyhydramnios	1	0.3	0	0.0
Anemia	4	1 1	0	0 0
Pelvic instability	3	0.8	12	3.2
Neurological symptoms	5	1.3	3	0.8
Others	3	0 8	8	2 1

Table I.8. *Signs of toxemia during the pregnancy of 378 mothers of children with unstable hips at birth (group A) and in 378 mothers of control newborns (group B)*

	Group A		Group B	
	No.	%	No.	%
Blood pressure >140/90	35	9.3	26	6.9
Proteinuria	12	3.	8	.1

Table I 9 *Infections during pregnancy of 378 mothers of children with unstable hips at birth (group A) and of 378 mothers of control newborns (group B)*

	Group A		Group B	
	No	%	No.	%
Urinary tract infections	39	10.3	29	7 7
Other specified infections	13	3 4	6	1.6
Unspecified infections	2	0.5	9	2.4

Table I 10 *Administration of drugs during pregnancy in 378 mothers of children with unstable hips at birth (group A) and in 378 mothers of control new borns (group B)*

	Group A		Group B	
	No.	%	No.	%
Antiemetics	7	1 9	3	0.8
Diuretics	26	6.9	17	4.5
Antibiotics	45	11.9	39	10.3
Hormones	5	1.3	3	0.8
Sedatives	4	1 1	2	0.5
Analgetics	0	0.0	1	0.3
Unknown drugs	5	1.3	5	1.3

statistically significant. Fig. I.3 illustrates the distribution of values in the two groups

Table I.23 shows the correlation of birth length and the gestational period for children with unstable hips and Table I.24 shows the corresponding values for children with stable hips. There is no statistically significant dif ference between the frequency of long for date and short for date babies between the groups A and B The increased number of children born after gestational periods exceeding 41 weeks fell within the 10-90 percentiles for length.

From Table I 25 can be seen that there was statistically significant difference between

Table I 11 *The birth presentation of 378 chil dren with unstable hips at birth (group A) and of 378 control new borns (group B)*

	Group A		Group B	
Presentation	[illegible]	%	No	%
Left occiput anterior	[illegible]	[illegible]	248	65 6
Right occiput anterior	[illegible]	[illegible]	103	77 2
Breech, left sacrum ant	4[illegible]	11	5	1 3
Breech, right sacrum post	[illegible]	[illegible]	1	0 3
Breech, unspecified	[illegible]		1	0 3
Footling, left sacrum ant			0	0 0
Footling, right sacrum post			[illegible]	0 0
Footling, unspecified		[illegible]	0	0 0
Left brow		[illegible]	[illegible]	3 2
Right brow	0	0	5	1 3
Not specified		0		0 8

Table I 12. *Induction of labour of 378 children with unstable hips at birth (group A) and 378 control new borns (group B)*

	Group A		Group B	
	No.	%	No.	%
Spontaneous	259	68.5	300	79 4
Oxytocin induction	67	17 7	49	13.0
Rupture of membranes	27	7 1	29	7 7
Vacuum extr Forceps	[illegible]8	7 4	[illegible]	3.2
Manual extraction	0	0.0	0	0.0
Caesarian section	20	5.3	7	1 9

the mean birth length of first born babies compared with second or later born babies

Table I.26 shows the mean head circumference of children with unstable and stable hips The difference between the two groups is statistically significant

Table I 27 compares the mean weight of the placenta of infants with unstable and with stable hips The difference between the two groups is statistically significant.

Fig. I 4 illustrates the correlation between the weight of the placenta and the birth weight of children with unstable hips, and Fig I.5 illustrates the corresponding correlation for children with stable hips As can be seen the correlations are poor (Corr coeff 0.58332 and 0 64521 respectively)

From Table I.28 can be seen that the ratio of placental weight to foetal weight (the "pla cental coefficient") is the same in affected and non-affected children

Table I.29 shows that the frequency of pathological placentas is the same in the patient group as in the control group

Table I.30 shows the Apgar score of children with unstable hips and Table I.31 shows the Apgar score of children with stable hips The small differences between the two groups are not statistically significant

Table I 32 shows the results of the luxation provocation test on the first or second day of life About one third of the children with instability of the hip displayed bilateral affec tion and among those unilateral affected in-

Table I 13 *Clinical data of 20 newborns with unstable hips delivered by Caesarian section*

Indications	Duration of pregnancy (weeks)	Presentation	Birth weight (g)	Birth length (cm)
Mechanical disproportions:				
Small pelvis	41	Vertex	3 580	49
Small pelvis	39	Vertex	3 600	52
Small pelvis	42	?	2 970	50
Small pelvis + malposition	40	Breech	2 790	45
Small pelvis + malposition	39	Breech	3 800	50
Small pelvis + malposition	40	Breech	3 870	50
Large baby + malposition	40	Breech	4 410	52
Large baby + malposition	42	Breech	4 610	55
Large baby + malposition	41	Breech	4 730	54
Large baby + malposition	42	Vertex	4 610	53
Large baby + malposition	41	Vertex	4 290	53
Pathological pregnancy or delivery				
Surdocardial syndrome	41	Breech	3 440	50
Previous Caesarian section	40	Vertex	4 070	53
Placenta praevia	37	Vertex	3 770	49
Slow progress of labour	42	Vertex	3 470	51
Slow progress of labour	43	Breech	3 840	53
Slow progress of labour	44	Breech	3 580	51
Foetal problems				
Bradycardia	40	Vertex	3 290	50
Low oestriol	40	Vertex	2 870	50

stability of the left hip was more frequent than that of the right

Table I.33 shows that of the 12 cases missed on the first examination ten had unilateral and two bilateral affection on the subsequent examinations

Table I.34 shows the sex distribution related to the affected side in children with unstable hips In girls bilateral affection occurred significantly more frequently than in boys

In Table I 35 is shown the correlation between the different vertex presentations and the affected hip Instability of the left hip appeared significantly more frequently in children born by the right occiput anterior presentation than in those born by the left occiput anterior presentation. Bilateral affection occurred significantly more frequently in children born by the non-vertex presentation than in those born by the vertex presentation.

Fig. I.6 illustrates the distribution of unilateral and bilateral affections of the hips

Table I 14 *Clinical data of seven newborns with stable hips delivered by Caesarian section*

Indications	Duration of pregnancy (weeks)	Presentation	Birth weight (g)	Birth length (cm)
Mechanical factors				
Small pelvis	39	Vertex	3 260	51
Large baby	42	Vertex	4 470	55
Pathological pregnancy or delivery				
Placenta praevia	36	Vertex	3 010	49
Toxaemia	37	Vertex	2 220	46
Diabetes	38	Breech	3 350	48
Slow progress of labour	43	Vertex	2 850	48
Previous child with CP	40	Breech	3 230	49

Table I 15 *Complications of delivery of 378 newborns with unstable hips (group A) and 378 control newborns (group B)*

	Group A		Group B	
	No.	%	No.	%
Bleeding	27	7 1	15	4 0
Pathological foetal heart beats	13	3 4	5	1.3
Meconium stained liquor	46	1[illegible]	26	6.9
Duration of delivery exceeding 24 hours	10	2.6	7	1 9
Liquor efflux before 12 hours ante partum	40	10.6	[illegible]5	6.6
Other complications	3	0.8	0	0.0

Table I 17 *The relation between the birth order and the mean gestational period in 358 children with unstable hips at birth (group A) and 352 control newborns (group B)*

	Group A			Group B		
Birth order	No	Mean (days)	S.D	No	Mean (days)	S D
1	181	286.97	10.05	142	[illegible]85.38	12.37
2 or >	177	285 46	10.74	10	282.37	11 74
Total	358	286.23	10.41	352	283.58	1[illegible].07

among the different weight groups and Fig. I 7 the corresponding distribution between the length groups It can be seen that the bilateral affection occurred more frequently in large babies than in the smaller ones

From Table I.36 can be seen that bilateral affection occurred more frequently in long children than in those of the shorter group provided that the A>B-hypothesis is adopted

Table I 37 shows the correlation between the affected side and duration of pregnancy No correlation could be shown

Table I.38 shows that at the age of one week 49 children out of 362 (13 per cent) still dis- [illegible]d unstable hips Nine of those children [illegible]3 per cent) originally had bilateral instability [illegible]ereas the remainder (10 per cent) originally were unilaterally affected

Table I 39 shows that the incidence of persistent instability at the age of one week was equally distributed among boys and girls

Table I 40 shows various pathological findings in newborns with unstable hips and newborns with stable hips There was no statistically significant difference between the two groups

Tale I 41 shows the frequency of associated malformations in children with unstable and stable hips Foot deformities occurred more frequently in the affected than in the non-affected group but the figures are too small for a definite evaluation

DISCUSSION

The Trondheim area offers good conditions for the investigation of the problems of congenital dislocation of the hip All children are delivered in two maternity clinics and examinations of the newborn are performed by few experienced pediatricians

In the examination of the newborn we used both the abduction test and the subluxation provocation test (9 59) We did not try to clas-

Table I 16. *The m[illegible]n [illegible]tati[illegible]nal period of 359 newborns with unstable hips (group A) and 353 control newborn[illegible] (g[illegible]up B)*

	Group A			Group B		
	Boys	[illegible]	Total	Boys	Girls	Total
No	85	[illegible]4	[illegible]9	82	271	353
Mean (days)	[illegible]86.41	[illegible]	[illegible] 17	28[illegible]1	284 01	283.59
S D	11 61	1[illegible]	10 44	1[illegible].50	11 91	12.06

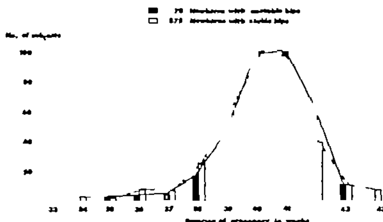


Fig. 1 1 The gestational period of children with unstable hips at birth and of control children.

sify unstable hips into "dislocated" and "dislocatable" as we had a strong impression that it depended largely on the position of the legs whether the hips were found in or out of joint at the time of the examination (9 28 39 71) "Atypical clicks" of the hip were not recorded as they seem to be without clinical significance (74)

The frequency of unstable hips in the present study was 19 03 per thousand liveborns Apart from data reported by Ramstad (65) and Harlem (32) the incidence in Trondheim is the highest reported in Norway (12 46 50) From other countries wide variations in the frequency of unstable hips in the newborn are reported Extremely high incidences from 160 to 240 per thousand are reported from Czechoslovakia (35 39) and relatively high incidences from Germany (2, 3) and Romania (21) The frequency of unstable hips in the present study is in accordance with figures given by James & Sevastikoglou (37) Barlow (10) and Medbo (46) Most authors report considerable lower incidences varying from 2 to 10 per thousand liveborns (12, 22, 25 28 29 33 50 59 60, 74 81) The incidence of unstable hips of newborn in Trondheim has shown a decreasing tendency during recent years and thus tendency seems to continue (16.2 per thousand in 1975 and 14.8 per thousand in 1976) Similar variations in the same district at different times have also been observed by others (70)

The variable results of the screening examinations of the newborn may be due to one or several different factors. The diagnosis of the instability is to some extent subjective depending upon the force and the technique used by the examiner Diagnosis may be missed for such reasons as inexperience difficult examination of a crying or a large baby dislocated irreducible hips or stable hips with the potential tendency to dislocate later (47 65 74 77) The figures must necessarily be influenced by the frequency of premature deliveries and in view of the results of the present study also by the frequency of pro-

Table I 18 *The mean birth eight of 378 children with unstable hips at birth (group A) and 378 c ontrol new borns (group B)*

	Boys			Girls			Total		
Group	No	Mean	S.D	No	Mean	S.D.	No.	Mean	S.D
A	90	3 673 22	479 18	288	3 605 45	502.55	378	3 6.1.59	497.30
B	90	3 574.56	573 .5	288	3 458.18	468.48	378	3 485.89	497 11

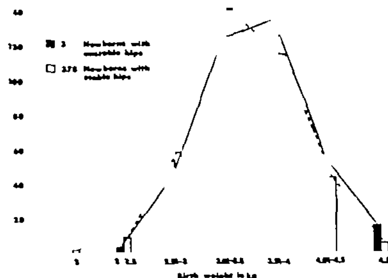


Fig 1.2 The birth weight of children with unstable hips at birth and of control newborns.

longed pregnancies In Finland Timonen could demonstrate that the duration of pregnancy was influenced among others, by geographical factors (76)

The high frequency of a positive family history of hip abnormalities in the group of children with unstable hips corresponds well with other reports (12 15 20 23 50 67) but it must be stressed that the present family history data are based on recollections of the parents, and the results must be considered with great causion

In contrast to other studies (23 36) the present investigation did not show any increased frequency of pathological findings during the pregnancy in the mothers of af

Table I 19 *Correlation of birth weight and gestational period in 340 children with unstable hips at birth*

	Duration of gestation			
...ight group	<37 weeks	37–41 weeks	>41 weeks	Total
<10 perc.	0	30	6	36 (10.6%)
10–90 perc.	3	10	52	265 (77 9%)
>90 perc	4	..9	6	39 (11.5%)
Total	7 (..1%)	..69 (79 1%)	64 (18.8%)	340 (100%)

Table 1.20 *Correlat n of birth weight and gestational period in 334 control newborns with stable hips*

	Duration of gestation			
Weight group	...	37–41 weeks	>41 weeks	Total
<10 perc		34	6	42 (1..6%)
10–90 perc.		..6	31	265 (79.3%)
>90 perc.		..0	3	..7 (8.1%)
Total	4 4	..0 (83 8%)	40 (1..0%)	334 (100%)

Table I.21 *Correlation between the birth order and the mean birth weight in 377 children with unstable hips at birth (group A) and 377 control new borns (group B)*

	Group A			Group B		
Birth order	No.	Mean (g)	S.D.	No.	Mean (g)	S.D
1	189	3 558.04	490.91	152	3 506.02	483 10
2 or >2	188	3 682.77	497.07	225	3 473.51	507 76
Total	377	3 620.24	497.27	377	3 486.62	497.57

Table I.22. *The mean birth length of 378 children with unstable hips at birth (group A) and 378 control new borns (group B)*

	Boys			Girls			Total		
Group	No.	Mean	S.D	No.	Mean	S.D.	No.	Mean	S.D.
A	90	51 49	1.95	288	50.81	2.07	378	50.97	2.06
B	90	51 41	2.49	288	50.36	2.02	378	50.61	2.18

fected children. This was also valid for the pelvic instability of the mothers Minor deviations from the normal course of pregnancy not detected on routine clinical examinations cannot of course be excluded Most previous reports on this topic are difficult to evaluate partly because of lack of control groups partly because of heterogenous groups of patients, mostly including the "late-diagnosis CDH" In spite of several characteristics in common with the group of children with unstable hips (12) the "late-diagnosis CDH" possibly constitutes a different clinical entity (part IV)

Apart from occasional exceptions (44) the low frequency of premature babies among children with unstable hips has been recognised for long (12, 50). The increased incidence with prolonged pregnancies demonstrated in the present series has not been reported previously

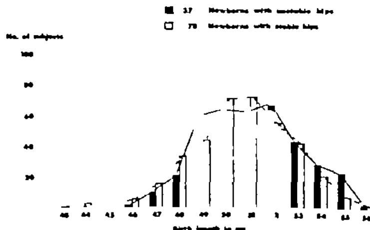


Fig I.3 The birth length of children with unstable hips at birth and control new borns.

Table I 23 *Correlation of the birth length and gestational period in 340 children with unstable hips at birth*

Length group	Duration of gestation <37 weeks	37–41 weeks	>41 weeks	Total
<10 perc.	0	41	7	48 (14.1%)
10–90 perc.	3	187	41	231 (67.9%)
>90 perc.	4	41	16	61 (17.9%)
Total	7 (2.1%)	269 (79.1%)	64 (18.8%)	340 (100%)

Based on thirty different investigations cited by Clifford (17) 50 to 60 per cent of all pregnancies have a duration between 280 and 290 days. The mean duration of pregnancy in the Norwegian population is 282±15 days (11). The incidence of pregnancies lasting between 290 and 295 days falls within the 10–16 per centile and in only 5 to 8 per cent does the duration of pregnancy exceed 295 days (17). Similar figures are given by Döring (24). Bakke (8) considers 294 days as the upper normal limit and states that 2.5 to 15 per cent of pregnancies exceed that limit.

In the present series the mean duration of pregnancy in the mothers of affected children was 286.17±10.44 and 73 of the mothers (45.9 per cent) had a duration of pregnancy above 294 days. It may be noted that even in the mothers of the control children the frequency of prolonged pregnancies was higher [illegible]n expected as 52 mothers (37.2 per cent) [illegible]d a duration of pregnancy greater than 294 days. This may indicate that the frequency of prolonged pregnancies in Trondheim generally is high and could be a possible explanation for the high frequency of unstable hips. Moreover the control group was not unselected with respect to the circannual distribution of birth dates of the children. The decreasing incidence of unstable hips observed in recent years might be explained by improved antenatal control and more rigorous indications for the induction of labour but the problem needs further investigations.

Even if the mechanism involved in the pathogenesis of prolonged pregnancy is unknown, changes in the hormonal balance of the mother are important (17). Timonen has demonstrated that the duration of pregnancy increases with increasing maternal age (76). In the present material the mean age of the mothers with prolonged pregnancy was not higher than the mean age of mothers with normal or short pregnancy.

Timonen also found that postmaturity was correlated with maternal overweight (76). This factor was unavailable for examination in the present study.

Table I.24 *C[illegible]rrelation of the birth length and gestational period in 334 control newborns [illegible]ith stable hips*

Length group	Duration of gestation [illegible] [illegible]eeks	37–41 week	>41 weeks	Total
<10 perc	1	35	10	46 (13.8%)
10–90 perc	10	206	22	238 (71.3%)
>90 perc	3	19	8	50 (15.0%)
Total	14 4	260 (83.8%)	40 (1[illegible]%)	334 (100%)

Table I.25 *The relation between the birth order and the mean birth length in 377 children with unstable hips at birth (group A) and 377 control newborns (group B)*

Birth order	Group A No.	Group A Mean (cm)	Group A S.D	Group B No.	Group B Mean (cm)	Group B S.D
1	189	50.87	2.02	152	50.73	2.04
2 or >2	188	51.06	2.10	225	50.54	2.28
Total	377	50.97	2.06	377	50.62	2.18

Table I.27 *The mean weight of the placenta of the placenta of 365 newborns with unstable hips (group A) and the placenta of 368 control newborns (group B)*

	Group A Boys	Group A Girls	Group A Total	Group B Boys	Group B Girls	Group B Total
No.	86	279	365	89	279	368
Mean (g)	671.34	676.53	675.30	647.4[illegible]	644.57	645.26
S D	131.69	142.22	139.65	121.[illegible]1	121.81	1[illegible]1.50

The search for etiological factors in postmaturity has hitherto been focused on the placenta. Quite recently Nwosu et al (57) have presented data which seem to indicate that postmaturity may represent a special foetal disorder. Significantly lower levels of neonatal plasma cortisol were found in postmature neonates, and the author ascribes the results to a possible foetal adrenal insufficiency. A common mechanism may well be responsible for both postmaturity and the laxity of the hip joint.

In spite of several investigations (1, 5, 7) the role of maternal hormones in the pathogenesis of unstable hips is still disputed. It has been shown that there is a considerable increase in the production of maternal hormones towards term (30) and a possible hormonal effect on the relaxation of the joint capsule will probably be accentuated in prolonged pregnancies, except in those cases where there is placental insufficiency. In the present series the incidence of mothers with signs of placental insufficiency or toxaemia was the same in the patient group and the control group. Neither was there any increased number of "dysmature" or "small-for-date" babies in the affected group of children.

The increased mean birth weight of girls in the present series is in agreement with Bjerkreims results (17). Bjerkreim found that girls with neonatal CDH had a significantly higher mean birth weight than girls in the control group and the late-diagnosis CDH girls, whereas no significant difference was observed in boys. In the series of children with CDH published by Record (67) and Robinson (69) the mean birth weight of the affected children was significantly lower than the birth weight of controls. In both cases the materials consisted of the so-called "late-diagnosis CDH".

The increased size of girls with unstable hips, expressed by the increased mean birth weight, birth length and head circumference is probably a consequence of the prolonged pregnancy. As no similar increase of the birth

Table I.26 *The mean head circumference of 373 children with unstable hips at birth (group A) and 373 control newborns (group B)*

Group	Boys No.	Boys Mean	Boys S.D.	Girls No.	Girls Mean	Girls S D	Total No.	Total Mean	Total S D
A	87	36.155	1.345	286	35.384	1 740	373	35 564	1 687
B	87	35 471	1.516	286	34 904	1 467	373	35 036	1 496

366 NEWBORNS WITH UNSTABLE HIPS

WEIGHT OF PLACENTA (G)

BIRTH WEIGHT (G)

CORRELATION COEFF.

Fig. 14. The correlation between the birth weight and weight of the placenta in children with unstable hips at

weight was observed in boys one must assume that the prolonged gestational period has different effects in boys and in girls, producing a laxity of the hip joint in both sexes and affecting the weight of girls only.

The increased size of the child might theoretically represent a contributory factor in the pathogenesis of unstable hips. Reduced movements and malpositions of the legs may cause increased pressure on the joint capsule producing similar conditions as are supposed to operate in the breech malposition. The "mechanical" theory might be supported by the in-

Table I.28. *The ratio of placental weight to foetal weight ("placental coefficient") of 365 newborns with unstable hips (group A) and in 368 control newborns (group B)*

	Group A			Group B		
	Boys	Girls	Total	Boys	Girls	Total
No.	86	279	365	89	279	368
Mean	0.18	0.19	0.19	0.18	0.19	0.19
S.D.	0.03	0.03	0.03	0.02	0.03	0.03

Table I.29. *Pathological placentas of 366 newborns with unstable hips (group A) and of 368 control newborns (group B)*

	Group A		Group B	
	No.	%	No.	%
Boys	10	11.6	7	7.9
Girls	31	11.1	27	9.7
Total	41	11.[illegible]	34	9.2

368 NEWBORNS WITH STABLE HIPS

WEIGHT OF PLACENTA (G)

BIRTH WEIGHT (G)

CORRELATION COEFF.

Fig. 15. The correlation between the birth weight and the weight of the placenta in healthy newborns.

Table I.30 *The Apgar score of 378 new borns with unstable hips*

Age (min)	Apgar score 0–4 No.	%	5–8 No.	%	9–10 No.	%
1	5	1.3	32	8.5	341	90.2
5	3	0.8	5	1.3	370	97.9
10	3	0.8	3	0.8	372	98.4

creased incidence of foot deformities, possibly due to increased intrauterine pressure in children with unstable hips. The difference of the mean birth weight of boys and girls is in opposition to this view Moreover the mechanical factors operating in breech malposition are unclear

The increased weight of placenta in children with unstable hips is probably also an expression of the prolonged pregnancy in spite of the weak correlation between placental weight and the birth weight The "placental index" however was the same in the affected as in the non-affected group of children. The findings fit well with the fact that the incidence of "small-for-date" or "dysmature" children in the group of newborn with unstable hips was within normal limits

The increased frequency of complicated deliveries in the affected group has been reported (23) but no reasons for the findings have been given previously The increased size of the child together with the increased

Table I.32. *Results of the examination of the hip joint performed by the author (KC) and the consultants of the Pediatric Clinic (O)*

Examiner	Side affected: Right No.	%	Left No.	%	Bilateral No.	%	Total
KC	67	26..	87	38.3	81	35.5	.35
O	36	26.3	63	42.9	44	30.8	143
Total	103	77.2	150	39 7	1.5	33 1	378

frequency of breech presentations offer good explanation for the results.

The similar results of the Apgar score in affected and non-affected children seem to indicate that the various procedures instituted in children with unstable hips were adequate and are an expression of good obstetrical service

In the present series 50 1 per cent of the children with unstable hips were first-born. The figure is in agreement with the incidences of 50–60 per cent given by various other authors (2 3 7 12 50) The various characteristics of children with unstable hips were equally distributed among the first-born and the second- or later-born children Hence the increased frequency of first-born children in the affected group is unclear and will be discussed in a separate study on breech presentations It may be mentioned that Timonen found significantly longer duration of pregnancy in the group of primiparae delivered of girls than in any other group (76)

Table I.31 *The Apgar score of 378 new borns with stable hips*

Age (min)	Apgar score 0–4 No.	%	5–8 No.	%	9–10 No.	%
1	9	2 4	20	5.3	349	92.3
5	6	1 6	4	1 1	368	97 4
10	6	1.6	1	0.3	371	98.1

Table I.33 *Distribution of cases with unstable hips missed on the first examination*

Examiner	Side affected: Right	Left	Bilateral	Total No	%
Author	5	2	0	7	3
Others	1	2	2	4	2.8
Total	6	4	2	12	3 2

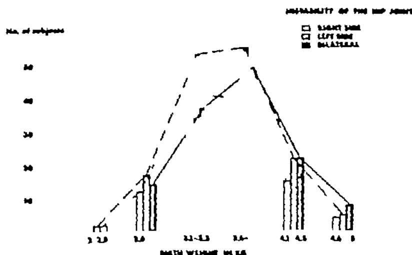


Fig 1.6 The distribution of unilateral and bilateral affections of unstable hips among different weight groups of children.

The present investigation included 93 boys (24 6 per cent) and 285 girls (75 4 per cent) The sex distribution is in accordance with that given by Lauritzen (40) Finlay (28) Ritter (68) or Fredenborg (29) One group of authors report incidences between 10 and 20 per cent for boys (26 33 34 50 59) whereas another smaller group present relatively high figures for boys ranging from 30 to 40 per cent (2 3 35 65) Bjerkreim (12) has found a higher percentage of boys in the group of children with atal CDH compared to the late-diagnosis As boys were generally less affected girls Bjerkreim states that the neonatal group may include a higher proportion of individuals with the tendency to revert to normal spontaneously Moreover the results of his studies indicate that high incidence in boys may be due to overdiagnosis

Table 1.34 *The side affected in 84 boys and 281 girls with unstable hips at birth*

	Side affected					
	Right		Left		Bilateral	
	No.	%	No	%	No	%
Boys	4	21.6	39	46 4	21	5 0
Girls	75	26.7	104	37 0	10[illegible]	36 3
Total	99	27 1	143	39 3	1[illegible]3	33.6

The distribution of unstable hips by side affected is in agreement with other neonatal studies although great variations have been noted The frequency of bilateral affection range from 22 per cent (46) to 50 per cent (29 50 79) lying most frequently between 30 and 40 per cent (12 26 28 31 35 40) Most of the authors have found the left side more often affected than the right although a few opposite results have been reported (33 34 46, 65)

In the present series the bilateral affection was significantly higher in girls than in boys. The same observation has been made by Fredensborg (29) but was not verified by Bjerkreim (12)



Fig 1.7 The distribution of unilateral and bilateral affections of unstable hips among different length group of newborns

Table I.35 *Correlation between the left occiput ant and right occiput ant presentation and the side affected*

	Side affected of unstable hips					
	Right		Left		Bilateral	
Presentation	No.	%	No.	%	No.	%
Left occiput ant.	65	28.9	86	38.2	74	32.9
Right occiput ant.	23	25.8	45	50.6	21	23.6
Not vertex	24	28.9	23	27 7	36	43 4

Table I.36. *Correlation between side affected and the birth length*

	Side affected of unstable hips					
Birth length (cm)	Right		Left		Bilateral	
	No.	%	No.	%	No.	%
41–45	0		1		2	
46–50	51	30.5	70	41 9	46	27.5
51–55	61	27.2	81	36.2	82	36.6

The present study seems to indicate a correlation between the right occiput anterior presentation and the affection of the left hip It has not been possible to find similar observations in the literature and the result is difficult to explain in view of the fact that left occiput anterior presentation is far more common (30).

Many authors have stressed the transitional character of the laxity of the hip joint (12 50 59) but only in one series was precise data

Table I.38. *The development of the instability of the hip joint in 362 children during the first week of life*

	Side affected		
	Right	Left	Bilateral
Initial examination	97	142	123
Subsequent examination			
Right	10		9
Left		15	6
Bilat.			9
O	87	127	99

Table I.39 *The sex distribution in infants with persisting instability of the hip joint at one week of life*

	Side affected				
				Total	
	Right	Left	Bi-lateral	No.	%
Boys	3	8	4	15	17.9
Girls	23	17	9	49	17 4

concerning the progress of the instability given (81)

In the present group of children with unstable hips 49 (13 per cent) still had a positive luxation provocation test at the age of one week. No further examination was performed in those children before the age of three months but at that time all subjects displayed stable hips It may be noted that the bilateral affection persisted more often than the one-sided affections (18 per cent and 10 per cent

Table I 37 *The duration of gestation by the affected side in children with unstable hips at birth*

	Duration of gestation in days					
	Boys		Girls		Total	
Affected side	Mean	S.D.	Mean	S D.	Mean	S.D
Right	282.95	15 12	285.39	10.69	284.82	11.83
Left	286.82	8.80	285.96	10.09	286.19	9 74
Bilateral	284.85	10.37	286.55	9.82	286.60	9.87

Table I 40 *Pathological findings of 378 new born babies with unstable hips (group A) and of 378 control new borns (group B)*

	Group A		Group B	
Pathological findings	No.	%	No.	%
Dysmaturity	12	3.2	8	2.1
Hypotonia	6	1.6	5	1.3
Irritability	4	1.1	3	0.8
Jaundice	32	8.5	32	8.5
Respiratory distress	1	0.3	0	0.0
Infections	1	0.3	0	0.0
Paresis	1	0.3	1	0.3

Table I 41 *The frequence of associated malformations in 378 new borns with unstable hips (group A) and 378 control new borns (group B)*

	Group A		Group B	
	No	%	No.	%
Foot deformities	9	2.4	0	0.0
Downs syndrome	1	0.3	0	0.0
Hypospadia	0	0.0	1	0.5
Others	1	0.3	0	0.0

respectively) If girls are generally more severely affected than boys (12) one would have expected to find increased frequency of persistent laxity in girls This could not be demonstrated in the present material Likewise it might have been expected that the bilateral affection would be present more frequently following long gestational periods than following those of shorter duration Neither of these assumption could be verified on the basis of the present results.

The results of the present series partly support the view that bilateral instability of the hip joint at birth is more serious and more persistent than the unilateral conditions occurs more frequently in large babies and more often in girls than in boys

It is noteworthy that in twelve cases in the present series the instability was not diagnosed on the first examination of the child In four cases different examiners were involved and different techniques might have been used In eight cases all examinations were performed by the same examiner and no explanation can be given for the results. A possible harmful effect of the luxation provocation test in a predisposed hip cannot be excluded.

II. BREECH MALPOSITION IN CHILDREN WITH UNSTABLE HIPS AT BIRTH

It is generally accepted that instability of the hip joints is much more frequent in children born by breech presentation than in those born by vertex presentation (7 10 12 28 35 46 59 65)

Nevertheless the majority of children born by breech presentation display stable hips The present study consists of a detailed analysis of the pre- and perinatal conditions affecting children born by breech presentation and an attempt to find possible differences between children with unstable hips and those with stable hips

MATERIAL AND METHODS

From 1.5 1969 to 31 12 1974 19864 children (10240 boys and 9624 girls) were born in the two maternity units in Trondheim (E C Dahls Stiftelse and the Obstetrical Department of the Regional Hospital) During this period instability of the hip joint was found in 378 children (93 boys and 285 girls) A detailed analysis of the pre- and perinatal condition of the children is presented in part I Of the children with unstable hips 68 were born by breech presentation (group A) This represents 18 per cent of the newborns with unstable hips and 3 4 per thousand of the total number of liveborns

The control group of children consisted of 262 newborns (136 boys and 126 girls) born by breech presentation at the E C Dahls Stiftelse maternity unit from 1 1 1970 to 31 12.1974 (group B) Of the 9320 liveborns during the same period this represents a frequency of 28.1 per thousand

Information concerning the prenatal and perinatal condition of the children was based on Hospital Records. Details of the data recorded are similar to those given

When computing the mean gestational period birth weight birth length head circumference and weight of the placenta the twins and the triplets were excluded from the material.

The collected data were processed in a UNIVAC 1108 at the Computing Centre of the University of Trondheim The mean values of group A and group B were computed Differences of means were tested by the t test, and P values below 0 05 were regarded as statistically significant. When indicated regression curves and confidence limits were computed Correlation coefficient >0 75 was regarded as positive.

RESULTS

Table II 1 shows the frequency of hip joint abnormalities in the families of children with unstable hips and in the families of children with stable hips. The difference between the two groups is statistically significant.

Table II.2 shows the frequency of other malformations in families of affected and non-affected children. The figures are too small for definite evaluations

Table II.3 shows the mean age of mothers in the two groups There is no statistically significant difference between the ages in group A and group B

Table II 4 shows the frequency of previous abortions or stillbirths in the mothers of group A and group B There is no statistically significant difference between the two groups

From Table II.5 can be seen that first-born children occurred significantly more frequently in group A than in group B There was also a significant difference of the frequency of children with birth rank three whereas there was no significant difference of the frequency of children with birth rank two

Table II 7 *Signs of toxaemia during the pregnancy of mothers of children born by breech presentation*

Group A. 68 mothers of children with unstable hips. Group B 262 mothers of children with stable hips

	Group A		Group B	
	No.	%	No.	%
Blood pressure above 140/90	4	5.9	.3	8.8
Proteinuria	2	2.9	20	7.6

Table II 8 *Signs of infection during the pregnancy of mothers of children born by breech presentation*

Group A. 68 mothers of children with unstable hips. Group B 262 mothers of children with stable hips

	Group A		Group B	
	No	%	No	%
Urinary tract infections	3	4 4	20	7.6
Other specified infections	1	1.5	1	0.4
Unspecified infections	0	0.0	9	3 4

Table II 9 *Administration of drugs during pregnancy to mothers of children born by h presentation*

oup A. 68 mothers of children with unstable hips. B 262 mothers of children with stable hips

	Group A		Group B	
Drugs	No.	%	No.	%
Antiemetics	1	1.5	8	3 1
Diuretics	0	0.0	.5	9.5
Antibiotics	5	7 4	'6	9.9
Hormone	2	2.9	5	1 9
Sedati es	0	0.0	1	0.4
Unknown	2	2.9	5	1.9

Fig. II 1 shows the distribution curves of the values including the values of twins.

Table II 17 shows the sex distribution of children born by breech presentation The incidence of girls was significantly higher in group A than in group B

Table II 18 shows the mean birth weight of children with unstable and stable hips The difference between the two groups is statistically significant for both boys and girls Fig II ? illustrates the distribution curves of the values including the values of twins

Table II 19 shows the correlation of birth weight and the gestational period in the two groups of children born by breech presentation As can be seen there is no difference in the frequency of "small for date" or "large for date" infants between the two groups The number of children born after a gestational period of 41 weeks was significantly higher in group A than in group B but those children fell within the 10–90 percentiles for weight

Table II.20 gives the mean values of the birth length of children with unstable and stable born by breech presentation The difference between the two groups is statistically significant for both boys and girls. Fig. II.3 illustrates the distribution curves of the values including the values of twins.

Table II.21 shows the correlation of birth length and the gestational period for children with unstable and stable hips born by breech presentation There is no statistically significant difference between the frequency of "long for date" and "short for date" infants between groups A and B

Fig. II 4 illustrates the correlation between

Table II 10 *The distribution of breech and footling presentations among children with unstable hips (group A) and among child en with stable hips (group B)*

	Breech			Footling			Total		
Group	Boy	Girl	Total	Boy	Girl	Total	Boy	Girls	Total
A	19	43	62		4	6	1	47	68
B	[illegible]	66	148	54	60	114	136	126	26.
Total	101	109	210	56	64	120	157	173	330

[illegible] and Sagg 'SI

Table II 11 *The distribution of different types of breech presentations in children with unstable hips (group A) and in children with stable hips (group B)*

	Group A		Group B	
Presentation	No.	%	No.	%
Breech, left sacrum ant.	45	66.2	113	43.1
Breech, right sacrum post.	16	23.5	32	12.2
Breech, unspecified	1	1.5	3	1 1
Footling, left sacrum ant.	3	4 4	90	34 4
Footling, right sacrum post.	3	4 4	23	8.8
Footling, unspecified	0	0.0	1	0.4
Total	68	100.0	262	100.0

the birth weight and gestational period of children with unstable and stable hips born by breech presentation. The values of twins are included in the figure.

Table II.22 shows the mean head circumference of children with unstable and stable hips The difference between the two groups is statistically significant both for boys and girls.

Table II.23 compares the mean weight of the placenta of infants in group A and group B The difference between the two groups was not statistically significant

Fig. II.5 illustrates the correlation between the weight of the placenta and the birth weight

Table II 12 *The course of delivery of 330 mothers of children born by breech presentation*

Group A 68 mothers of children with unstable hips. Group B. 262 mothers of children with stable hips

	Group A		Group B	
Delivery	No.	%	No.	%
Spontaneous	33	48.5	165	63 0
Oxytocin induction	13	19 1	40	15.3
Rupture of membranes	2	2.9	9	3 4
Vacuum or Forceps.	17	25.0	35	13 4
Manual extraction	0	0.0	23	8 8
Caesarian section	9	13.2	14	5.3

Table II.13 *Clinical data of nine children with unstable hips born by breech presentation and Caesarian section*

Indication for Caesarian section	Duration of pregnancy (weeks)	Birth weight (g)	Birth length (cm)
Mechanical			
Small pelvis	40	2 790	45
Small pelvis	39	3 800	50
Small pelvis	40	3 870	50
Large infant	40	4 410	52
Large infant	42	4 610	55
Large infant	41	4 730	54
Slow progress	43	3 840	53
Slow progress	44	3 580	51
Disease of mother	41	3 440	50

of children with unstable hips and Fig. II.6 illustrates the corresponding correlation for children with stable hips As can be seen the correlations are poor (Corr coeff 0 60642 and 0 42683 respectively)

From Table II.24 can be seen that the ratio of placental weight to foetal weight (the "pla-

Table II 14 *Clinical data of fourteen children with stable hips born by breech presentation and Caesarian section*

Indication for Caesarian section	Duration of pregnancy (weeks)	Birth weight (g)	Birth length (cm)
Mechanical			
Small pelvis	44	2 910	48
Small pelvis	7	2 900	48
Small pelvis + large infant	40	4 380	52
Small pelvis	40	4 040	51
Small pelvis	43	4 070	52
Malposition	42	3 900	52
Malposition	39	2 790	49
Pathological pregnancy or delivery			
Placenta praevia	39	3 320	52
Placenta praevia	39	3 340	50
Slow progress	40	3 700	50
Postmaturity	42	2 840	48
Danger of uterine rupture	40	3 640	52
Fetal problems			
Bradycardia	39	2 520	49
Bradycardia	38	2 340	47

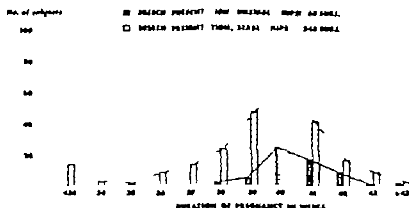


Fig II 1 The gestational period in children born by breech presentation with unstable and stable hips at birth.

cental coefficient") was higher in children with stable hips than in children with unstable hips. The difference was not statistically significant

Table II.25 shows that the frequency of pathological placentas was significantly higher in boys and nearly significantly higher in girls of B than of group A

Table II.26 shows the Apgar score of children with unstable hips and Table II.27 shows the Apgar score of children with stable hips. Infants of the latter group obtained significantly lower Apgar score than the infants in the former group

Table II.28 shows various pathological findings in children born by breech presentation There was no statistically significant difference between the infants with unstable hips and those with stable hips

Table II.29 shows the frequency of associated malformations in children with unstable and stable hips born by breech presenta-

Table II 15 *Complications of delivery of 330 mothers of children born by breech presentation*

Group A. 68 mothers of children with unstable hips. Group B 76. mothers of children with stable hips

Complications	Group A		Group B	
	No.	%	No	%
Bleeding	4	5 9	17	6.5
Pathological foetal heart beats	3	4 4	10	3.8
Meconium stained liquor	5	7 4	18	6.9
Duration of delivery > 4 hours	2	2 9	1	0 4
Liquor efflux 1 hours before partu	11	16 2	34	13 0
Other complications	1	1 5	1	4 6

Table II 17 *The sex distribution of children born by breech presentation*

Group A. 68 children with unstable hips. Group B 262 children with stable hips

	Group A		Group B	
	No.	%	No	%
Boys	21	30.9	136	51 9
Girls	47	69 1	126	48 1
Total	68	100 0	26.	100 0

Table II 16 *The mean gestation period of children born by breech presentation*

Group A. 63 children with unstable hips Group B 209 children with stable hips

Group	Boys No.	Girls Mean	S D	Total No.	Mean	S D
A	70	286 07	7 84	63	285 36	9 66
B	105	279 61	14.35	209	278 69	17 61

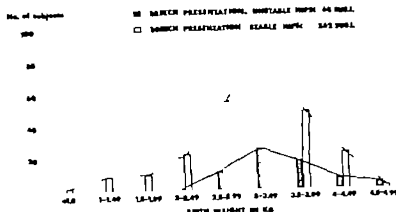


Fig II.2 The birth weight of children born by breech presentation with unstable and stable hips at birth.

tion. Foot deformities occurred more frequently in the affected than in the non-affected group but the figures are too small for a definite evaluation.

Table II.30 shows the incidence of multiple births in children born by breech presentation Whereas the incidence of twins and triplets among children with stable hips was 15.3% there was only one twin (1.5%) in the group of children with unstable hips.

DISCUSSION

Although the frequency of breech presentation is high in all series of children with unstable

Table II.18. *The mean birth weight of children born by breech presentation*

Group A. 67 newborn with unstable hips. Group B 222 newborn with stable hips

	Boys			Girls			Total		
Group	No.	Mean	S.D.	No.	Mean	S.D.	No.	Mean	S.D
A	20	3 576.50	503.09	47	3 432.55	571.21	67	3 475.52	552.01
B	112	3 243.30	791 49	110	3 104.36	607.85	222	3 174.46	708.33

Table II 19 *Correlation of birth weight and gestational period in 255 children born by breech presentation*

Group A 60 children with unstable hips. Group B. 195 children with stable hips

	Gestational period			
Weight group	<37 weeks	37–41 weeks	>41 weeks	Total
Group A				
<10 perc	0	11	1	12 (20%)
10-90 perc	1	35	6	42 (70%)
>90 perc	0	4	2	6 (10%)
Total	1 (1 7%)	50 (83.3%)	9 (15.0%)	60 (100%)
Group B				
<10 perc	5	41	6	52 (26.7%)
10-90 perc	6	116	9	131 (67.2%)
>90 perc	3	8	1	12 (6.2%)
Total	14 (7.2%)	165 (84.6%)	16 (8.2%)	195 (100.0%)

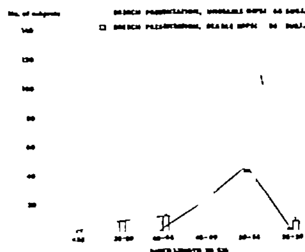


Fig. II.3 The birth length of children born by breech presentation with unstable and stable hips at birth.

hips at birth the data given by different authors vary considerably. Relatively low incidences between 4 and 8% are given by Artz et al. (7) Bjerkreim (12) Njå (50) and Ramstad (65) Barlow (10) Medbo (46) and Palmén (59) give frequencies between 10 and 20% whereas Salter (72) Ackermann (2) and Finlay (28) report incidence over 20%. The highest frequencies of 30% and 33% are presented by Rutter (68) and Huttová et al. (35) respectively. The frequency of breech presentation among children with unstable hips is high also in the present study (20.2%).

No satisfactory explanation can be given for the great range of incidence of breech presentation in the different series. Theoretically the frequency of premature deliveries may have some influence upon the figures. As shown by Braun et al. (13) the general frequency of breech deliveries at term is 3.1%. Prior to 37 weeks of gestation the frequency is twice as great as in full-term pregnancies and three times as great for infants with a birth weight under 2.5 kg. As prematurity seems to give a relative protection against instability of the

Table II.20 *The mean birth length of children born by breech presentation*
Group A. 67 newborns with unstable hips. Group B. 222 newborns with stable hips

	Boys			Girls			Total		
Group	No.	Mean	S.D.	No.	Mean	S.D	No.	Mean	S.D
A	20	51.05	1.90	47	50.53	2.54	67	50.69	2.37
B	112	49.64	4.06	110	49.[illegible]3	3.04	222	49.44	3.59

Table II.21 *Correlation of birth length and gestational period in 255 children born by breech presentation*
Group A. 60 children with unstable hips. Group B. 195 children with stable hips

	Gestational period			
Length group	<37 weeks	37–41 weeks	>41 weeks	Total
Group A				
<10 perc.	0	9	1	10 (16.7%)
10–90 perc.	1	34	4	39 (65.0%)
>90 perc.	0	7	4	11 (18.3%)
Total	1 [illegible]	50 (83.3%)	9 (15.0%)	60 (100.0%)
Group B				
<10 perc.		36	4	45 (22.6%)
10–90 perc.		10[illegible]	11	1[illegible]4 (63.6%)
>90 perc.			1	26 (13.8%)
Total	1	1[illegible] (84.6[illegible])	16 (8.[illegible]%)	195 (100.0%)

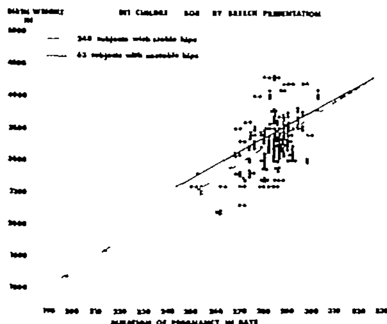


Fig II 4 The correlation of gestational period and birth weight of children born by breech presentation.

hips high frequency of premature deliveries would give low percentage figures for unstable hips combined with high percentage of breech presentations. However the different incidences of breech presentation among children with unstable hips given for different parts of Norway (Oslo 4% Trondheim 20%) makes this explanation rather unsatisfactory

Although there is a general agreement that breech presentation is an important factor in the aetiology of congenital dislocation of the hip (CDH) the mechanism of pathogenesis is still obscure. Three different theories have been proposed.

The marked flexion of the hips acts through a distension of the joint capsule, especially when combined with failure of the leg-folding mechanism (13 27 83)

Table II 22. *The mean head circumference of children born by breech presentation*
Group A. 66 newborns with unstable hips. Group B 220 newborns with stable hips

	Boys			Girls			Total		
Group	No	Mean	S.D	No.	Mean	S.D.	No.	Mean	S.D
A	19	36.684	1.216	47	35.404	1.647	66	35 773	1.634
B	111	35.212	2.912	109	34 716	[illegible].128	220	34.966	2.560

Table II.23 *The mean weight of placenta of children born by breech presentation*
Group A 67 children with unstable hips. Group B. 220 children with stable hips

	Boys			Girls			Total		
Group	No	Mean	S.D	No.	Mean	S.D	No.	Mean	S.D
A	20	667 .5	162.83	47	663 72	158.20	67	664.78	158.37
B	11	658 71	156.58	108	625.65	145.70	220	642.48	151.90

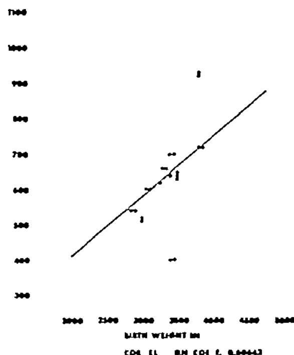


Fig II.3 The correlation of birth weight and weight of the placenta in children with unstable hips born by breech presentation.

The breech posture represents only one of *the multiple factors in the pathogenesis* female sex hormones being of equal importance (82)

There must be a common, more fundamental mechanism responsible for both the laxity of the hip joint and the breech malposition (13) The following conditions are of special interest Multiple joint dislocation (Larsens

Table II.25 *Pathological placentas of 3?7 children born by breech presentation*

Group A. 68 children with unstable hips. Group B. ?59 children with stable hips

	Group A		Group B	
	No	%	No	%
Boys	1	5.0	25	18.5
Girls	4	8.5	19	15.3
Total	5	7.4	44	17.0

syndrome) neuromuscular diseases (Prader Willys syndrome Zellweger syndrome myotonic dystrophy Werdnig-Hoffmans syndrome) and congenital laxity of the hip joint In all these conditions breech presentation occurs more frequently than would be expected and possibly the disorders themselves limit the ability of the foetus to alter its position in utero According to this concept the breech malposition would represent a secondary phenomenon to the laxity of the hip joint

The results of the present study seem to favour one of the last two theories.

The following characteristics appeared more frequently in the group of children with unstable hips than in the group with stable hips. *familial occurrance of hip abnormalities* female sex birth rank one complications of delivery including use of forceps or vacuum extractor and Caesarian section prolonged gestational period increased mean birth weight birth length and head circumference

The fact that the same characteristics have been shown to occur more frequently in the

Table II 4 *The rati f pla ental weight (f foetal weight (" placental coefficient") in children born by breech presentation*

Group A. 67 newborns with unstable hips Group B 220 newborn with stable hips

	Boy			Girl			Total		
Group	No.	Mean	[illegible]	N	Mean	S D	No	Mean	S D
A	?0	0 19	0 ?4	?4	0 19	0 04	67	0 19	0 04
B	11	0 1	0	10?	0 1	0 05	?20	0 1	0 05

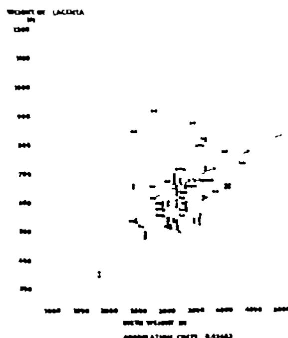


Fig. II.6. The correlation of birth weight and weight of the placenta in children with stable hips born by breech presentation.

total series of children with unstable hips in contrast to the group of control children (part I) strongly supports the view that breech presentation represents only a part of a complex mechanism and additional factors are most probably necessary for the production of manifest laxity of the hip Among these factors interest must be focused upon the gestational period and the size of the child possibly due to hormonal disorders of the mother It may however be admitted that the prolonged gestational period may be of less importance in the children born by breech presentation compared with the whole group of children with unstable hips as the frequency of gestational period exceeding 294 days was 16.4% in the former group and 45 9% in the latter (part I)

If the breech presentation per se should represent a great risk for the development of CDH one would expect to find a relatively high percentage of cases born by breech presentation among the so-called "missed" cases of CDH It is noteworthy that among the "missed" cases in Trondheim during a period of five years only one was born by breech presentation and two by footling presentation (part IV) This corresponds to the normal occurrance of breech presentations in the control group of children

Observations made in one child not included in the present material illustrate some of the

Table II.26 *The Apgar score of 68 children with unstable hips born by breech presentation*

Age of the child (min)	Apgar score 0–4		5–8		9–10	
	N	%	No	%	No.	%
1	3	4 4	13	19 1	52	76.5
5	1	1.5	2	2.9	65	95.6
10	1	1 5	2	2.9	65	95.6

Table II 27 *The Apgar score of 262 children with stable hips born by breech presentation*

Age of the child (min)	Apgar score 0–4		5–8		9–10	
	No.	%	No.	%	No.	%
1	15	5 7	80	30.5	167	63 7
5	7	2.6	29	11 1	226	86.3
10	6	2.2	17	6.5	239	91.2

Table II.28 *Pathological findings in 330 children born by breech presentation*

Group A. 68 children with unstable hips. Group B: 262 children with stable hips

Symptoms and signs	Group A No	Group A %	Group B No.	Group B %
Dysmaturity	2	2.9	16	6.1
Hypotonia	1	1.5	6	[illegible]
Irritability	1	1.5	6	2.3
Paresis	1	1.5	1	0.4
Jaundice	12	17.6	29	11 1
Respiratory distress	0	0.0	2	0 8
Infections	1	1.5	0	0.0

Table II.29 *The frequency of malformations in 330 children born by breech presentation*

Group A. 68 children with unstable hips. Group B 262 children with stable hips

	Group A		Group B	
Malformations	No	%	No.	%
Foot deformities	3	4 4	0	0 0
Syndactylia	0	0.0	4	1.5
Hydrocephalus	0	0.0	1	0.4
Downs syndrome	1	1.5	0	0 0
Others	1	1.5	1	0.4

above mentioned problems On examination of a 24 year old pregnant woman (para II) breech malposition was diagnosed four weeks prior to delivery An external version of the foetus was performed and the child was subsequently born by a normal vertex presentation. The birth weight was 3 860 g birth length 51 cm and the head circumference 36.5 cm. The duration of gestation was estimated to 285 days There was a distinct instability of the right hip on the first day after birth but stable hips on the sixth day If the breech posture per se had produced such an injury to the hip that ould last for four weeks one would not expect the instability to disappear within one week of delivery

It has been postulated that the higher incidence of birth rank one in children with CDH is mostly due to the association between birth rank one and breech presentation (1?) The results of the present study do not confirm this assumption as the incidence of birth rank one was significantly higher in the group with unstable hips than in the group with stable hips The role of birth order in the pathogenesis of unstable hips remains obscure

The distribution of the different types of breech presentation in the two groups is interesting. Whereas the children with unstable hips were born by the breech left sacrum anterior presentation in 66 the frequency of breech left sacrum anterior and footling left sacrum anterior presentati n was 43% and 34% respectively in the gr up with stable hips Only 4 4% of children with unstable hips were born by footling left sacrum anterior presentation The results seem to indicate that the incomplete breech malposition (footling malposition) represents a relatively small risk for the development of unstable hips

No data on the relative frequency of the different types of breech presentations (frank or complete) could be obtained from the Hospital Records

Fettweis (27) states that only the frank breech presentation with hips maximally flexed and knees extended is associated with unstable hips According to his opinion the pressure exerted on the posterior rim of the acetabulum in this position represents an important pathogeneic factor in the production of dysplasia.

Wilkinson (82) suggests that the breech malposition is due to a delay of the peripheral nerve development of the lower extremities In most cases the delay is supposed to be physiological" but may be pathological as in spina bifida. In the frank breech malposition the week dorsiflexion muscles allow the foot to be moulded into equinovarus and the medial rotation of the leg leads to femoral anteversion The more common complete breech malposition produces a lateral rotation and a posterior dislocation of the hip

The present investigation did not show any increased frequency of pathological findings during the pregnancy of mothers of affected children On the contrary the increased use of

Table II.30 *Multiple births of children born by breech presentation*

Group A. 68 children with unstable hips. Group B 262 children with stable hips

	Group A		Group B	
	No.	%	No	%
First twin	1	1.5	15	5 7
Second twin	0	0.0	22	8.4
Triplet	0	0 0	3	1.2
Total	1	1.5	40	15.3

diuretics by mothers of children with stable hips seems to indicate an increased frequency of milder forms of toxaemia in a greater proportion of mothers of children with stable hips

The increased frequency of complicated deliveries in mothers of children with unstable hips is probably an expression of the increased size of the children combined with the malposition In spite of the increased incidence of various procedures instituted in the newborns with unstable hips the Apgar score was significantly higher in this group compared with the group of children with stable hips. The difference is most likely due to the increased frequency of premature deliveries in the group of children with stable hips

The characteristics of the placentas in the two groups of children under discussion need a few comments. The increased mean weight of placenta demonstrated in the whole group of children with unstable hips (part I) is probably an expression of the prolonged pregnancy The difference of the mean weight of placenta in the two groups born by breech presentation was not statistically significant. As both the mean gestational period birth weight, birth length and head circumference was significantly higher in children with unstable hips the findings of the placenta are difficult to explain. The increased frequency of pathological placentas in children with stable hips is remarkable and one cannot exclude a possible connection between this finding and the increased frequency of premature infants in this group

III SEASONAL VARIATION OF BIRTHS DATES OF INFANTS WITH UNSTABLE HIPS AT BIRTH

In 1955 Nagura (49) reported a seasonal variation in the incidence of infants with congenital dislocation of the hip (CDH) Since then similar observations have been made in many countries (6 12 16 45 63 67 69 78 81) In spite of several proposed theories no satisfactory explanation for the seasonal fluctuation has as yet been given

The purpose of the present study was to investigate possible seasonal variation of some of the factors which are known to occur with increased frequency in children with CDH

MATERIAL AND METHODS

The material comprises the following groups of subjects

Group A 108 infants with unstable hips diagnosed at the Maternity Hospital of Trondheim (E C Dahls Stiftelse) from 1 1 1963 to 31 12.1968 During this period examination of the hip joint of the newborns was performed by a pediatric consultant twice a week. 9 children were examined on the first day 26 on the second day 20 on the third day 26 on the fourth day 17 on the fifth day and 10 on the sixth day after birth Table III 1 shows the chief clinical data relating the patients

Group B 397 infants (95 boys and 302 girls) diagnosed at the two maternity units of Trondheim (E C Dahls Stiftelse and the Obstetrical Department of the Regional Hospital) from 1.5 1969 to 1.5 1975 During this time all newborns were examined by a small number of senior consultants of the Pediatric Clinic on the first or second day of life About 15000 infants were examined by the author Except for 19 infants with unstable hip diagnosed in 1975 details of the group are pre ed in part I

Group Bb 75 infants (2 and 53 girls) with unstable hips born by e h presentation These children are included in the total number of subjects of group B Except for 7 infants diagnosed in 1975 a detailed description of this group of children is presented in part II

Group C 43 children (16 boys and 27 girls) with stable hips at birth and late-diagnosis CDH born from 1 1 1970 to 31 12 1974 Detailed data of the patients are presented in part IV

Group D 262 infants (136 boys and 126 girls) with stable hips born by breech presentation at the Maternity Hospital of E C. Dahls from 1 1 1970 to 31 12 1974 Clinical data of the infants are dealt with in part II

Group E 336 control newborn of the same sex born chronologically next to the children of group B All these children presented stable hips at birth. Detailed data of the group except for those born in 1969 are presented in part I

Group F 326256 newborns in Norway from 1 1 1967 to 31 12.1971 with known duration of the gestational period This material was divided into three groups according to the mother s county of residence Southern Norway included the following counties. Østfold Akershus Oslo Hedmark, Oppland, Buskerud Vestfold Telemark, Austagder Vest agder and Rogaland Mid-Norway included the counties Hordaland Sogn and Fjordane More and Romsdal Sor Trondelag and Nord-Trondelag. Northern Norway included three counties. Nordland Troms and Finnmark.

Group G 315637 newborns in Norway from 1 1 1970 to 31 12 1974

Group H 421 pregnant women treated for toxaemia in Trondheim from 1 1 1970 to 31 12 1974

The following data were recorded.

The seasonal variation of birth dates of chil-

Table III 1 *Children with unstable hips diagnosed in Trondheim from 1 1 1963 to 31 12 1968*

Year of birth	No. of patients	No. of liveborns	Incidence of infants with unstable hips per 1 000 liveborns
1963	9	461	3.66
1964	26	2 652	9.90
1965	19	2 745	6.92
1966	21	2 859	7.31
1967	20	765	7.23
1968	13	3 051	4.26
Total	108	16 533	6 5
Boys	29 (26.9 %)		
Girls	79 (73 1 %)		
Breech presentation	10 (9.3 %)		

dren in groups A B Bb C and D in relation to the total number of liveborns

The seasonal variation of birth dates of boys and girls in group B

The seasonal variation of birth dates of first born children in groups B and E

The mean length of the gestational period related to the month of birth for infants of group G

The seasonal variation of birth dates of infants with gestational period exceeding 294 days in group B E and F

The months of admission of women in group H

The mean monthly temperature (Table III.2) the absolute duration of sunshine (Table III.3) and the relative duration of sunshine (Table III 4) in Trondheim from 1969 to 1974 were based on observations from the Norvegian Meterlological Institute (51 52, 53 54 55 56)

The collected data were processed in a UNIVAC 1108 at the Computing Centre of the University of Trondheim. Statistical calculations were performed with the chi-square analysis and P values below 0 05 were regarded as statistically significant

RESULTS

Table III.5 shows the observed and expected frequency of newborns with unstable hips in Trondheim from 1 1 1963 to 31 12 1968 (group A) The hypothesis of equal distribution of birth dates of infants with unstable hips for the different months could not be rejected

Table III 6 shows the variation of birth dates of infants in group A according to warm mild and cold seasons The birth dates were equally distributed between the different seasons

The variation of birth dates of infants of group A according to light moderately illuminated and dark seasons is shown in Table III 7 No statistically significant variation between the seasons could be demonstrated

Table III 2. *The mean monthly temperature in Trondheim from 1969 to 1974*

Months	Year 1969	1970	1971	1972	1973	1974	Mean
January	−2 1	−5 5	−1.0	−4 9	2.5	1.6	−1.6
February	6.3	−7.5	−0.4	−1.5	−2.1	0.2	−2.8
March	2 8	−0.9	2 2	1 9	3.3	1.4	0.1
April	4.5	1 7	3 1	3 9	1 7	4.5	3.2
May	8 7	9 3	9 7	9.4	7.8	9.5	9 1
June	14.1	14 4	10.9	13 7	11.9	12.7	13.0
July	13 3	14.9	13 0	15 1	14.2	12.2	13.5
August	17 1	13 7	12.8	12.8	11.6	12.5	13 4
September	8 5	9 1	8.9	7.8	8.3	10.9	12.3
October	6 0	6.0	4.9	5.0	3.2	3 7	4.8
November	1 9	−1 0	0 6	1.2	−1.2	0.0	0.9
December	3	−0.4	2.0	2.7	−1.5	0.3	0.0

Table III.3 *The mean monthly duration of sunshine in Trondheim from 1969 to 1974 in mean number of recorded hours of sunshine*

Month	1969	1970	1971	1972	1973	1974	No. of possible hours of sunshine
January	41.5	68.0	31 1	62.2	23.5	22.3	176.7
February	133 7	94 1	60.2	107.6	77.5	72.4	44.5
March	198.0	140.7	94.3	132.0	82.0	207.5	362.7
April	182.0	183.8	162.7	171 7	139.3	136.6	449.5
May	311 4	279.9	231.6	228.2	189 4	338.9	562.1
June	273.5	313.5	165 1	219.3	255 0	276.0	616.0
July	155.8	143 7	200.3	252.6	157.6	171 4	601 4
August	307 4	172.1	180.2	168.6	114 1	211.5	504.8
September	115 1	119.8	94 0	80.6	116.7	142.1	391.5
October	59.9	61.2	59.3	62.7	58.7	97.0	309 0
November	36.6	62.2	35 4	23 7	15 4	82.6	202.5
December	45 1	3 4	5 7	.3 0	2.6	26.1	142.6

From Table III 8 can be seen the observed and expected frequency of newborns with unstable hips in Trondheim from 1.5 1969 to 1.5 1975 (group B) The hypothesis of equal distribution of affected children for the different months was rejected ($P<0\ 01$) For the months September October and November the observed values were higher and for January lower than the expected values.

Fig. III 1 illustrates the frequency of newborns with unstable hips in Trondheim from 1 5 1969 to 1.5 1975 related to the mean monthly temperature and the relative duration of sunshine

Fig III 2 illustrates the seasonal variation of birth dates of the total number of affected children together with the mean temperature and absolute illumination during the period 1 5 1969 to 1.5 1975

Table III.9 shows the incidence of birth dates of infants of group B in relation to warm, mild and cold seasons The hypothesis of equal distribution of values was very narrowly rejected ($P<0\ 041$)

Table III 10 shows the frequency of newborns of group B in light moderately illuminated and dark seasons The hypothesis of

Table III 4 *The relative duration of sunshine in Trondheim from 1969 to 1974*

Relation in per cent between the recorded hours of sunshine and the maximum possible hours of sunshine

Month	Year 1969	1970	1971	1972	1973	1974
January	23.5	38.5	17 6	35.2	13.3	12.6
February	54 7	38.5	4 6	44.0	31 7	29.6
March	54 6	38 8	26 0	36.4	22 6	57.2
April	40.5	40 9	36 2	38 2	31 0	30.4
May	55 4	49 8	41	40 6	33 7	60.3
June	44 4	50 9	6 8	35 6	41 4	44.8
July	25.9	23.9	33 3	42 0	26.2	28.5
August	60.9	34 1	3 7	33 4	22 6	41 9
September	29 4	30.6	4	20 6	29.8	36.3
October	19 4	19.8	19	20 3	19 0	31 4
November	18.1	30.7	1	1 7	07.6	40.8
December	32.3	02.4	04	1	01 8	18 3

Table III.5 *Seasonal variation of birth dates of children with unstable hips in Trondheim from 1963 to 1968*

Month of birth	No. of liveborns	No. with unstable hips	Incidence per 1 000 liveborns	Expected no. with unstable hips
January	1 358	9	6.6	8.87
February	1 205	8	6.6	7.87
March	1 500	11	7.3	9.80
April	1 630	7	4.3	10.65
May	1 453	12	8.3	9 49
June	1 367	8	5 9	8.93
July	1 367	9	6.6	8.93
August	1 357	9	6.6	8.86
September	1 435	10	7 0	9.37
October	1 403	10	7 1	9 16
November	1 196	4	3.3	7.81
December	1 262	11	8.7	8.24
Total	16 533	108	6.5	107 98

Table III 6. *Birth date of infants with unstable hips in Trondheim from 1963 to 1968 in relation to warm and cold seasons*

Season of birth	No. of live-borns	No. with unstable hips	Incidence per 1000 live-borns	Expected no. with unstable hips
Dec., Jan., Feb.	3 825	28	7.3	24.9
March, April, May	4 583	30	6.5	29.9
June, July Aug.	4 091	26	6.4	26.7
Sept., Oct., Nov	4 043	4	5.9	26 4
Total	16 533	108		107.9

Table III 8. *Observed and expected frequency of new borns with unstable hips in Trondheim from 1.5 1969 to 1.5 1975*

Month of birth	No of li borns	No. of children with unstable hips	Frequency per 1000 live-borns	Expected no of children with unstable hips
January	1 768	19	10.7	33 4
February	1 686	38	22.5	31.9
March	1 915	38	19.8	36 2
April	1 967	35	17 8	37.2
May	1 858	34	18.3	35 1
June	1 800	26	14.4	34 0
July	1 717	29	16.9	3..5
August	1 693	33	19.5	32.0
September	1 7?4	50	29 0	32.6
October	1 649	44	26.7	31...
November	1 590	4	15 1	30.1
December	1 647	77	16.4	31 1
Total	21 014	397	18.9	397.3

equal distribution of values was rejected with high significance ($P<0\ 001$)

Table III.11 and Fig. III.3 show the seasonal variation of birth dates of boys and girls. The hypothesis of equal distribution of values was rejected for girls but not for boys.

The birth dates of boys related to light and dark seasons can be seen from Table III 1? The hypothesis of equal distribution of incidences could not be rejected

From Table III 13 can be seen the birth dates of girls of group B in relation to seasons with different illumination. The hypothesis of equal distribution of birth dates was rejected with high significance ($P<0.005$) The highest frequency of birth dates was observed in the moderately illuminated months August September and October

Table III 14 shows the seasonal fluctuation of birth dates of infants of group B born by different presentations The hypothesis of

Table III 7 *Birth dates of infants with unstable hips born in Trondheim from 1963 to 1968 in relation to light and dark seasons*

Season of birth	No of live-borns	No with unstable hips	Incidence per 1000 live-borns	Expected no. with unstable hips
Febr March, April	4 335	26	6.0	28.3
May June July	4 187	29	6.9	27 4
Aug., Sept Oct.	4 195	29	5 6	27 4
Nov Dec Jan.	3 186	.4	6 3	4 9
Total	16 533	108		108 0

Table III.9 *Birth dates of infants with unstable hips in relation to warm and cold seasons*

Season	No. of live-borns	No. with unstable hips	Frequency per 1000 live-borns	Expected no. with unstable hips
Dec., Jan., Feb.	5 101	84	16.5	96.36
March, April, May	5 740	107	18.6	108.43
June July Aug	5 210	88	16.9	98.4
Sept. Oct., Nov	4 963	118	.3.8	93 73
Total	1 014	397	18 89	396.96

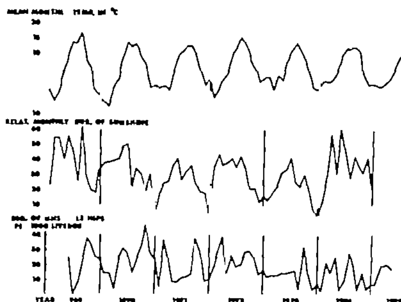


Fig III 1 The incidence of 397 newborns with unstable hips the mean monthly temperature and the relative duration of sunshine in Trondheim from 1.5 1969 to 1.5 1975

equal distribution of values was narrowly rejected for infants born by vertex presentation ($P<0\ 0375$) and rejected with high significance for those born by breech presentation ($P<0\ 005$)

The birth dates of infants of group Bb in relation to seasons with different temperature is shown in Table III 15 The hypothesis of equal distribution of values could not be rejected on the level 0 05

Table III 16 shows the birth dates of infants of group Bb in relation to seasons with different illumination. No statistically significant fluctuation could be demonstrated

In Table III 17 are compared the monthly variations of birth dates of infants born by breech presentation with those born by footling presentation (group D)

Table III 18 shows the frequency of birth dates of infants of group D in relation to seasons with different illumination. The hypothesis of equal distribution of values could not be rejected

Fig III 4 illustrates the seasonal variation of

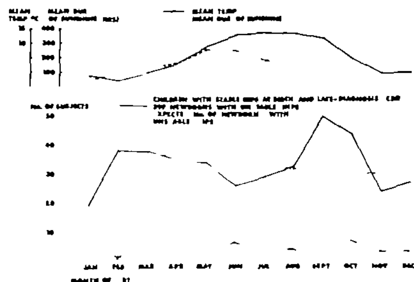


Fig III.2 The seasonal variation of birth dates of 397 infants with unstable hips and 43 infants with stable hips and late-diagnosis *CDH* the mean temperature and the mean absolute duration of sunshine during the period 1.5 1969 to 1.5 1975

Table III 10 *Birth dates of infants with unstable hips in relation to light and dark seasons*

Season	No. of live-borns	No. with un-stable hips	Frequency per 1000 live-borns	Expected no with unstable hips
Febr., March, April	5 568	111	19.9	105.2
May June, July	5 375	89	16.6	101.6
Aug., Sept. Oct.	5 066	127	25.1	95.8
Nov., Dec. Jan.	5 005	70	14.0	94.6
Total	21 014	397	18.9	397.2

Table III 1? *Variation of birth date of boys with unstable hips in relation to light and dark seasons*

Season of birth	No. with un-stable hips	No of live-borns	Incidence per 1000 live-borns	Expected no with unstable hips
Febr March April	31	2 844	10 9	4 92
May June July	19	2 806	6.8	4.58
August, Sept., Oct	28	2 561	10.9	22.44
Nov Dec. Jan.	17	2 633	6.5	23 07
Total	95	10 844		95.01

birth dates of different groups of infants born by breech presentation.

Table III 19 shows the seasonal variation of birth dates of first-born infants in group B No seasonal fluctuation of birth dates could be demonstrated.

Table III.20 shows the frequency of birth dates of first-born infants of group B related to warm, mild and cold seasons No seasonal fluctuation could be demonstrated.

Table III.21 shows the incidence of birth dates of first-born infants in light, dim and dark seasons The hypothesis of equal distribution of incidences could not be rejected.

From Table III.22 can be seen the seasonal variation of birth dates of first-born children of group E. No statistically significant fluctuation could be demonstrated

Table III.23 shows that there is no statistically significant seasonal fluctuation of birth-dates of first-born infants in Norway from 1 1 1970 to 31 12.1974

Table III 11 *Seasonal variation of birth date of boys and girls with unstable hips at birth*

Month of birth	Boys: No. of liveborns	Boys: No. with unstable hips	Boys: Expected no. with unstable hips	Girls: No. of liveborns	Girls: No. with unstable hips	Girls: Expected no. with unstable hips
January	947	5	8.30	821	14	24 38
February	874	12	7 66	812	26	4.11
March	1 009	10	8.84	906	28	26 90
April	961	9	8.42	1 006	26	29.87
May	979	7	8.58	879	27	26.10
June	898	3	7.87	902	23	26.79
July	929	9	8.14	788	20	23 40
August	857	8	7 51	836	25	24.83
September	863	8	7.56	861	42	25.57
October	841	1	7.37	808	32	23.99
November	850	8	7 45	740	16	21 97
December	836	4	7.32	811	23	4.08
Total	10 844	95	95 02	10 170	302	301.99

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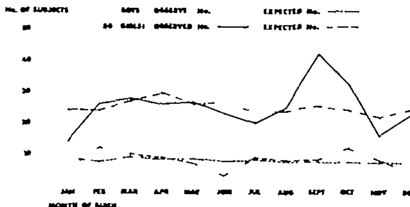


Fig III.3 The seasonal variation of birth dates of 95 boys and 302 girls with unstable hips in Trondheim from 1.5 1969 to 1.5 1975

The seasonal variation of birth dates of children of group B with different duration of the gestational period is shown in Table III 24

From Table III 25 can be seen the incidence of birth dates of infants of group B with gestational periods of different duration in relation to seasons with different temperature There was no statistically significant difference in the distribution of values between the infants with prolonged gestational period and infants with normal or short gestational period

Table III.26 shows the incidence of birth dates of infants of group B with different gestational periods in relation to seasons with different illumination There was no statistically significant difference in the distribution of values between the two groups and no seasonal fluctuation of values in the group of infants with prolonged gestational period

Table III.27 shows the incidence of birth dates of infants of group E with prolonged gestational period in relation to seasons with different temperature. No seasonal fluctuation of birth dates could be shown.

From Table III.28 can be seen the incidence of birth dates of infants of group E with prolonged gestational period in relation to seasons with different illumination The hypothesis of equal distribution of values could not be rejected.

In Table III.29 the birth dates of infants of group G are related to seasons with different illumination The mean gestational period of those born in the winter months was significantly lower than the mean gestational periods for the remaining seasons

Table III.30 shows the seasonal variation of birth dates of infants in Southern Norway with gestational period exceeding 294 days. The hypothesis of equal distribution of prolonged gestational periods was rejected ($P<0.005$)

From Table III 31 can be seen the seasonal variation of birth dates of infants in Mid-Norway with gestational period exceeding 294 days The hypothesis of equal distribution of cases was rejected with high significance ($P<0.001$)

The seasonal variation of birth dates of infants in Northern Norway with gestational period exceeding 294 days is shown in Table

Table III 13 *Variation of birth date of girls with unstable hips in relation to light and dark seasons*

Season of birth	No with unstable hips	No. of live-borns	Incidence per 1000 live borns	Expected no. with unstable hips
Febr March, April	80	2 724	2.94	80.89
May June July	70	2 569	2 72	76 29
August, Sept. Oct.	99	2 505	3 95	74.39
Nov Dec. Jan.	53	2 372	2.23	70.44
Total	302	10 170	2 97	302 01

Table III 14 *Seasonal variation of birth dates of infants with unstable hips born by different presentations from 1.5 1969 to 1.5 1975*

		Birth presentation			
		Breech		Vertex	
Birth month	No. of liveborns	Observed no	Expected no	Observed no.	Expected no
January	1 768	3	6.31	16	27.09
February	1 686	9	6.02	29	25.83
March	1 915	9	6.84	29	29.34
April	1 967	7	7.02	28	30.14
May	1 858	10	6.63	24	28.47
June	1 800	0	6.43	26	27.58
July	1 717	7	6.13	22	26.31
August	1 693	6	6.04	27	25.94
September	1 724	14	6.15	36	26.42
October	1 649	3	5.89	41	25.27
November	1 590	1	5.68	23	24.36
December	1 647	6	5.88	21	25.24
Total	21 014	75	75.02	322	321 99

III.32. No statistically significant fluctuation could be shown.

The results of Tables III.30 III 31 and III.32 are illustrated in Fig. III.5

Table III.33 shows the seasonal variation of birth dates of infants with stable hips and late-diagnosis CDH (group C) The hypothesis of equal distribution of values could not be rejected.

Table III.34 shows the frequency of toxaemia of pregnancy recorded in different months in Trondheim from 1 1 1970 to 31 12 1974 The difference between the highest incidence in May and the lowest incidence in December is statistically significant but apart from this no significant seasonal fluctuation could be demonstrated.

DISCUSSION

In 1955 Nagura (49) reported from Japan that 43 per cent of 1306 infants with CDH were born in December–January Similar observations on 217 affected children were made by

Table III 15 *Birth dates of infants with unstable hips born by breech presentation in relation to warm and cold seasons*

Season	No of liveborns	No of affected infants	Expected no of affected infants
Dec., Jan., Feb.	5 101	18	18.21
March, April, May	5 740	26	20.49
June, July Aug.	5 210	13	18.60
Sept., Oct. Nov	4 963	18	17 72
Total	21 014	75	75.02

Table III 16. *Birth dates of infants with unstable hips born by breech presentation in relation to light and dark seasons*

Season	No. of liveborns	No. of affected infants	Expected no. of affected infants
Febr., March, April	5 568	25	19.88
May June, July	5 375	17	19 19
Aug. Sept., Oct.	5 066	23	18 06
Nov., Dec., Jan.	5 005	10	17.87
Total	21 014	75	75.00

Table III 22 *Seasonal variation of birth dates of first-born children with stable hips*

Month of birth	No.	% of total	Expected no.
January	9	52.9	6.88
February	13	40.6	[illegible].95
March	13	41.9	12.55
April	10	33.3	12.14
May	11	40.7	10.93
June	10	38.5	10.52
July	10	37.0	10.92
August	11	39.3	11.33
September	16	39 0	16.59
October	16	44 4	14.57
November	6	30.0	8.10
December	11	52.3	8.50
Total	136	40.5	136.00

Table III 24 *Seasonal variation of birth dates of children with unstable hips and different duration of the gestational period*

Month of birth	Gestational period >294 days		<294 days	
	No.	%	No.	%
January	5	8.2	11	4.3
February	8	13 1	23	8.9
March	1	1.6	30	11.6
April	7	11.5	23	8.9
May	4	6.6	22	8.5
June	4	6.6	20	7.8
July	4	6.6	20	7.8
August	9	14.8	17	6.6
September	9	14.8	31	12.0
October	7	11.5	25	9.7
November	3	4.9	15	5.8
December	0	0.0	21	8.1
Sum	61	100.0	258	100.0

tors in the pathogenesis of late-diagnosis CDH this factor seems to be without significance in the present series

No satisfactory explanation can be given for the different results of the various series but several theories may be proposed One cannot exclude the possibility that some series of late-diagnosis CDH include variable numbers of children with unstable hips at birth either "missed" or not examined at all Such series must necessarily influence the corresponding series of neonatal CDH The results of the early series of the present material (children born from 1963 to 1968) seem to favour this hypothesis. Moreover it has been shown that prolonged gestational period represents one of the most important factors of the pathogenesis of unstable hips (part I) and the significant seasonal and regional variation in the occurrence of prolonged gestations demonstrated in the present study offers another attractive hypothesis for the seasonal variation of unstable hips

Table III 23 *Birth months of first born children in Norway from 1970 to 1974*

Month of birth	Year of birth 1970		1971		1972		1973		1974	
	No.	%	No.	%	No.	%	No.	%	No.	%
January	2 171	8.5	145	8.0	236	8.5	2 292	9 1	2 174	8.8
February	1 845	7.2	005	7.5	122	8.0	2 041	8.1	1 929	7.8
March	48	8.8	2 311	8.7	2 418	9.2	2 169	8.6	2 246	9 1
April	355	9.2	2 402	9 0	2 364	9 0	2 234	8.8	2 257	9 1
May	2 [illegible]31	8 7	2 473	9.3	2 47	8.5	2 131	8.4	2 181	8.8
June	141	8 3	2 [illegible]02	8.2	164	8.2	2 072	8.2	2 077	8.4
July	084	8 1	252	8 4	2 187	8.3	2 127	8 4	2 081	8.4
August	11	8	[illegible]50	8.4	2 196	8.3	2 120	8.4	2 078	8.4
September	4[illegible]	8 7	254	8.4	2 131	8.1	2 090	8.3	2 075	8.4
October	2 09[illegible]	8 2	2 183	8.[illegible]	2 091	7 9	2 017	8.0	1 988	8.0
November	1 951	7 6	2 082	7.8	2 094	7 9	1 958	7 7	1 809	7.3
December	2 209	8 6	141	8 0	119	8.0	2 043	8.1	1 910	7 7
Total	25 684		26 700		26 369		25 294		24 805	

Table III.25 *The frequency of children with unstable hips and different duration of the gestational period in relation to warm and cold seasons*

	Gestational period				
	>294 days		<294 days		
Months of birth	No.	% of total	No.	% of total	Total
Dec. Jan., Febr	13	19.1	55	80.9	68
March, April, May	12	13.8	75	86.2	87
June, July Aug.	17	23.0	57	77.0	74
Sept., Oct., Nov	19	21.1	71	78.9	90
Total	61	19.1	258	80.9	319

At least two seasonal factors may be of importance for the fluctuation of birth dates of affected children. Attention has hitherto been focused on the environmental temperature (16 67). The relatively constant body (and intra uterine) temperature under normal circumstances would seem to limit the importance of this factor. Seasonal fluctuation of birth dates have been reported from countries with widely differing climates. It may also be noted that in some places the highest incidence has been observed in winter (81) whereas others have observed the highest frequency in the autumn (6). However it has been demonstrated that prematurity gives relative protection against unstable hips (12) and some reports indicate a significantly increased frequency of premature deliveries in the cold season (66). The results of the whole Norwegian material from 1970 to 1974 seem also to point in the same direction.

The other factor of possible importance for the seasonal variation not mentioned previously is the illumination. The effect of light upon various hormonal functions in man (86)

Table III.26 *The frequency of children with unstable hips and different duration of the gestational period in relation to light and dark seasons*

	Gestational period				
	>294 days		<294 days		
Months of birth	No	% of total	No.	% of total	Total
Febr March, April	16	17.4	76	82.6	92
May June, July	12	16.2	62	83.8	74
August, Sept. Oct.	25	25.5	73	74.5	98
Nov Dec. Jan.	8	14.5	47	85.5	55
Total	61		258		319

Table III.27 *Seasonal variation of birth dates of children with stable hips (group E) and gestational period exceeding 294 days in relation to warm and cold seasons*

Season	Total no	No. of gestations >294 days	%	Expected no.
Dec., Jan., Febr	67	8	11.9	10.1
March April, May	86	14	16.3	13.0
June, July Aug.	73	15	20.5	11.1
Sept. Oct. N	91	11	12.1	13.8
Total	317	48		48.0

Table III.28 *Seasonal variation of birth dates of children with stable hips (group E) and gestational period exceeding 294 days in relation to light and dark seasons*

Season	Total no.	No. of gestations >294 days	%	Expected no.
Febr March, April	89	13	14.4	13.5
May June, July	76	12	15.8	12.5
Aug., Sept. Oct.	96	15	15.6	14.5
Nov., Dec., Jan.	56	8	14.3	8.5
Total	317	48		48.0

tex presentation. This may indicate that in periods of increased frequency of unstable hips there is also a relative increase of the most seriously affected infants.

The analyses of toxaemia of pregnancy in Trondheim during a five years period did not reveal any seasonal fluctuation in frequency These results are in agreement with studies of groups B and E (part I) which did not confirm reported observations of increased frequency of toxaemia in mothers of newborn with unstable hips (23)

IV PRENATAL AND PERINATAL CHARACTERISTICS OF CHILDREN WITH STABLF HIPS AT BIRTH AND LATE DIAGNOSIS CONGENITAL DISLOCATION OF THE HIP

It has been a common observation that a small group of children with congenital dislocation of the hip (CDH) has escaped diagnosis in the neonatal period in spite of routine examination by the luxation provocation test These so-called "missed cases" of CDH have been the subject of great interest in medical literature, but despite several proposed theories no satisfactory explanation for these cases has so far been accepted

The purpose of the present study was to analyse the prenatal and perinatal condition of the "missed cases" of CDH in Trondheim during a five year period.

MATERIAL AND METHODS

From 1.5 1969 to 31 12.1974 19864 children (10240 boys and 9624 girls) were born in the two maternity units in Trondheim. All were examined at least twice the first examination being performed on the first or second day of life and the second generally four to six days after birth About 15000 children were examined by the author the remainder by one of the consultants of the Pediatric Clinic Palméns and Barlows modification of Ortolani test was employed (9 58 60)

In the course of the five and a half year period instability of the hip joint was found in 378 children (group B) This group is described in detail together with a control group in part I

During the same period 44 children were referred to the Orthopedic Department of the Regional Hospital with signs of CDH (group A). Table IV 1 shows the sex distribution and incidence of both groups of children.

All the patients with late-diagnosis CDH presented stable hips at birth. Fourteen were examined on the first day twenty-six on the second day and four on the third day of life

Table IV.2 shows the reason for diagnosis and age at commencement of treatment in the children with late-diagnosis CDH Table IV.3 shows the clinical and radiological findings and Table IV 4 the treatment instituted.

Information regarding prenatal and perinatal condition of the children was based on Hospital records. Details of the data recorded are similar to those described in part I

The collected data were processed in a UNIVAC 1108 at the Computing Centre of the University of Trondheim The statistical methods employed have been described in part I

RESULTS

Table IV.5 shows the frequency of hip joint abnormalities in the families of late-diagnosis CDH-children and the hip joint abnormalities in families of children with unstable hips. The difference between the two groups is statistically not significant

Table IV 6 shows the mean age of the mothers in the two groups There is no statistically significant difference between groups A and B

Table IV 7 shows the frequency of previous abortions or stillbirths in the mothers of group A and group B There is no statistically significant difference between the two groups

From Table IV.8 can be seen that first born children occurred more frequently in group B than in group A but the difference was statistically not significant.

Table IV.9 shows the frequency of various symptoms and signs during pregnancy of mothers of children with late-diagnosis CDH

Table IV 1 *The incidence of late-diagnosis CDH and instability of the hip joint in Trondheim from 1.5 1969 to 31 12 1974*

	Boys		Girls		All		Incidence per thousand liveborns
	No	%	No.	%	No.	%	
Late-diagnosis CDH	16	36.4	28	63.6	44	100	2.21
Unstable hips	93	24 6	285	75 4	378	100	19.54

and of mothers of children with unstable hips at birth The differences between the two groups are statistically not significant

Table IV 10 shows the frequency of toxaemia in mothers of the two groups of children. Elevated blood pressure appeared significantly more often in group A than in group B whereas the different occurrence of proteinuria was statistically not significant.

From Table IV 11 can be seen the occurrence of different infections in mothers of children with late-diagnosis CDH and in mothers of children with unstable hips Unspecified infections were recorded more frequently in group A whereas the frequency of urinary tract infections was significantly higher in group B

The administration of drugs to the mothers shown in Table IV 12 Mothers of children unstable hips received antiemetics and antibiotics significantly more often than mothers of children with late-diagnosis CDH

Table IV 13 shows the birth presentation of children in groups A and B On the basis of B > A hypothesis the difference of left breech presentation (left sacrum anterior) between group A and group B is statistically significant

Table IV 14 shows the frequency of special procedures during the delivery of children with late-diagnosis CDH and children with unstable hips The difference between the two groups was statistically not significant.

Table IV 15 shows the indications for various procedures during the delivery of the two groups of mothers In three cases the indication was mechanical disproportions.

Table IV 16 shows the different complications of delivery for the two groups of children Early efflux of liquor appeared significantly more often in group A than in group B Otherwise there was statistically no significant difference between the two groups

The mean gestational period of children with late-diagnosis CDH and the mean gesta-

Table IV.2 *Reasons for diagnosis and age at start of treatment in children with late-diagnosis CDH*

	Age at start of treatment in months				
Reasons for diagnosis	0–3	4–6	7–12	12	Total
Limping or asymmetry observed by parents	3	5	2	3	13
Routine infant examination	7	10	3		20
Incidental examination		4	1		7
Familial occurrence			1		1
Uncertain findings at birth		1			3
Sum	14	20	7	3	44

Table IV.3 *The clinical and radiological findings in children with late-diagnosis CDH*

	No
Clinical findings	
Restricted abduction	27
Shortening of the leg	13
Asymmetrical skin folds	8
Radiological findings	
Signs of dysplasia	26
Subluxation or luxation	18

Table IV 4 *The treatment of children with late-diagnosis CDH*

	No.
Abduction splint	2
Plaster cast	40
Plaster cast + derotational osteotomy	2
Total	44

tional period of children with unstable hips is shown in Table IV 17 The difference between the two groups is statistically highly significant ($P<0\ 01$) for girls but not significant for boys

Fig. IV 1 illustrates the distribution curves of values for children with unstable hips control newborns and children with late-diagnosis CDH

Table IV 18 shows the mean birth weight of children with late-diagnosis CDH and the mean birth weight of children with unstable hips. The difference between the two groups is statistically significant for girls but not for boys

Table IV 19 shows the correlation of birth weight and the gestational period in the children with late-diagnosis CDH The frequency of small-for-date" and "large-for-date" babies was the same as in the group of children with unstable hips (10)

Table IV.20 gives the mean values of the birth length of children in groups A and B The difference between the two groups was statistically significant for girls but not for boys The difference between the total number of children in the two groups was statistically highly significant ($P<0\ 01$)

Table IV.21 shows the correlation of birth length and the gestational period for children with late-diagnosis CDH The frequency of "short-for-date" and "long-for-date" babies is statistically not different from the group of children with unstable hips (part I)

Table IV.22 shows the mean head circumference of children with late-diagnosis CDH and of children with unstable hips at birth The difference between the two groups is statistically significant for both boys and girls

Table IV.23 compares the mean weight of placenta of infants in groups A and B The difference between the two groups is statistically significant for girls only

Fig. IV.2 illustrates the correlation between the weight of the placenta and the birth weight of the late-diagnosis CDH-children As can be seen the correlation is poor (corr coeff 0 67032)

Table IV.5 *Abnormalities of the hip joint in families of 44 children with late-diagnosis CDH (group A) and in families of 378 children with unstable hips at birth (group B)*

	Boys			Girl			All		
Relatives	CDH	Other hip abnorm.	Sum	CDH	Other hip abnorm.	Sum	CDH	Other hip abnorm.	Sum
Group A									
1st degree	0	0	0	2	0	2	2	0	2
Others	0	2	2	5	6	11	5	8	13
Sum	0		2	7	6	13	7	8	15 (34.1%)
Group B									
1st degree	9	1	10	30	1	31	39	2	41
Others		3	10	28	9	37	35	12	47
Sum	16	4	20	58	10	68	74	14	88 (23.2%)

Table IV 6 *The mean age of mothers of children with late-diagnosis CDH (group A) and mothers of children with unstable hips at birth (group B)*

	Boys			Girls			Total		
Group	No.	Mean	S D	No	Mean	S.D	N	Mean	S.D.
A	16	[illegible]	4 45	28	27.39	5 03	44	26.61	4.89
B	89	25.01	4 42	228	25.92	5 44	377	25 70	5.23

Table IV 7 *Previous abortions of mothers of children with late-diagnosis CDH (group A) and previous abortions of mothers of children with unstable hips at birth (group B)*

	No. of abortions									
	0		1		2		3		Total	
Group	No	%	No.	%	No.	%	No.	%	No.	%
A	35	79.5	7	15.9	2	4.5	0	0.0	9	20.4
B	333	88.1	33	8.7	10	2.6	2	0.5	45	11 8

From Table IV.24 can be seen that the ratio of placental weight to foetal weight (the "placental coefficient") is the same in group A and in group B

Table IV.25 shows that the frequency of pathological placentas is the same in the two groups A and B

Table IV.26 shows the Apgar score in children with late-diagnosis CDH On average those children obtained lower score than the children with unstable hips but the differences are not statistically significant

Table IV.27 shows various pathological findings in children of groups A and B Instability was noticed significantly more often in children with late-diagnosis CDH than in children with unstable hips but for the rest there was statistically no difference between the two groups

Table IV.28 shows the frequency of associated malformations in children of group A and in children of group B The foot deformities occurred significantly more often in children with late-diagnosis CDH than in children with unstable hips at birth

Table IV.8 *The birth order of children with late-diagnosis CDH (group A) and children with unstable hips at birth (group B)*

	Group A		Group B	
Birth order	No.	%	No	%
1	18	40 9	189	50.0
2	12	27 3	105	27.8
3	7	15 9	47	12.4
4	3	6 8	23	6.1
5	4	9 1	8	2.1
6 or more	0	0.0	5	1 4

Table IV 9 *Various symptoms during the pregnancy of mothers of children with late-diagnosis CDH (group A) and mothers of children with unstable hips at birth*

	Group A		Group B	
	No.	%	No.	%
Emesis	1	2.3	11	2.9
Early bleeding	3	6.8	10	2.6
Late bleeding	2	4 5	4	1 1
Anemia	2	4.5	4	1 1
Pelvic instability	1	2.3	3	0.8
Tests of placentary function	1	2.3	1	0.3
Nervous symptoms	0	0.0	5	1.3
Diabetes	1	2.3	1	0.3
Rhesus incompatibility	0	0.0	2	0.5

Table IV 10 *Signs of toxemia during the pregnancy of mothers of children with late-diagnosis CDH (group A) and mothers of children with unstable hips at birth (group B)*

	Group A		Group B	
	No.	%	No	%
Blood pressure above 140/90	10	22.7	35	9.3
Proteinuria	3	6.8	12	3.2

In Table IV.29 are summarized the chief characteristics of children with late-diagnosis CDH and of the children with unstable hips at birth.

DISCUSSION

The incidence of the so-called "missed cases" of CDH as given by different authors varies considerably Barlow (9) and Artz (7) report 0 1 to 0.3 per thousand liveborn. Another group of investigators give figures between 0.4 and 1 per thousand (2, 3 29 37 46 50) The incidence of missed cases in the present series corresponds to the results presented by Ramstad (65) and Bjerkreim (12)

The "missed cases" included in the different series probably represent heterogenous groups of patients owing to one or several of the following factors.

The examination of the newborn might have been unsatisfactory due to an inexperienced examiner inadequate technique or difficult examination of a crying or a large infant (47). The examination might have been performed too late, as the optimal time of examination seems to be within the first two days of life (29) Children with dislocated irreducible hips might have been overlooked (48). There may be a special group of children with stable hips at birth and a potential tendency to develop dysplasia, subluxation or luxation at a later stage In this group of children the term "missed" is obviously mis-leading and should be omitted.

Table IV 11 *Signs of infection during the pregnancy of mothers of children with late-diagnosis CDH (group A) and mothers of children with unstable hips at birth (group B)*

	Group A		Group B	
	No	%	No.	%
Urinary tract infections	0	0.0	39	10.3
Other specified infections	0	0 0	13	3.4
Unspecified infections	6	13.6		0.5

Table IV 12. *Administration of drugs during pregnancy to mothers of children with late-diagnosis CDH (group A) and mothers of children with unstable hips at birth (group B)*

	Group A		Group B	
	No.	%	No	%
Antiemetics	0	0.0	7	1 9
Diuretics	1	2.3	26	6.9
Antibiotics	0	0.0	45	11 9
Hormones	2	4.5	5	1.3
Sedatives	0	0.0	4	1 1
Unknown	7	15.9	5	1.3

Table IV 13 *The birth presentation of 44 children with stable hips and late-diagnosis CDH (group A) and 378 children with unstable hips at birth (group B)*

	Group A		Group B	
Presentation	No.	%	No.	%
Left occiput anterior	25	56.8	217	57 4
Right occiput anterior	13	29.5	83	22.0
Breech, left sacrum ant.	1	2.3	45	11.9
Breech, right sacrum post.	0	0.0	16	4.2
Breech, unspecified	0	0.0	1	0.3
Footling, left sacrum ant.	0	0.0	3	0.8
Footling, right sacrum post.		4.5	3	0.8
Footling, unspecified	0	0.0	0	0.0
Left brow	1	2.3	0	0.0
Right brow	1	2.3	2	0.5
Not specified	1	2.3	2	0.5

Table IV 14 *The course of delivery in mothers of children with late-diagnosis CDH (group A) and in mothers of children with unstable hips at birth (group B)*

	Group A		Group B	
	No.	%	No.	%
Spontaneous	31	70.5	259	68.5
Oxytocin induction	8	18.2	67	17 7
Rupture of membranes	1	2.3	27	7 1
Vacuum extr forceps	3	6.8	28	7 4
Manual extraction	2	4.5	0	0.0
Caesarian section	2	4.5	20	5.3

Table IV 16 *Complications of delivery in children with late-diagnosis CDH (group A) and unstable hips at birth (group B)*

	Group A		Group B	
	No	%	No	%
Bleeding	2	4.5	27	7 1
Pathological fetal heart beats	3	6.8	13	3 4
Meconium stained liquor	3	6.8	46	12.2
Duration of delivery over 24 hours	2	4.5	10	2.6
Liquor efflux exceeding 12 hours before partus	10	22.7	40	10.6
Other complications	1	2.6	3	0.8

The series under discussion should represent a group of patients particularly suitable for analysis for the following reasons All children included in the study were born in one of the two maternity units of the region the examination was performed by a small number of experienced pediatricians and except for four children who were examined on the third day all examinations were performed within the first two days after birth Thus the influence of the first two factors responsible for the "missed" diagnosis should be minimal

Three patients displayed restricted movements of the lower extremities even from birth d might belong to the third category of issed cases However none of them presented luxation or subluxation of the hip when the treatment was started

The majority of cases consequently fall into the fourth category of patients.

In about fifty per cent of the patients the diagnosis of CDH was made on routine examination in infant health centres In about thirty per cent abnormal motor development was noticed by the parents The figures are in agreement with observations made by Palmén & von Rosen (62) and Bjerkreim (12) In sixteen per cent of the patients the diagnosis was made on incidental examination In three children pathological hips were observed on urograms performed for investigation of recurrent urinary tract infections in three the hip was radiographed because of various foot deformities and in one child hip examination was performed on account of a meningomyelocele.

One of the factors complicating the evaluation of the present series is a possible over diagnosis of CDH Palmén has recently stressed the important fact that some infants may show asymmetrical development of the hip owing to the habitual oblique position

Table IV 15 *Indications for various procedures instituted during the delivery of mothers of children with late-diagnosis CDH*

	Indications					
Procedures	Small-pelvis	Mal-position	Fetal distress	Post maturity	Slow progress	Toxemia
Sectio caesarea	1		1			
Forceps		2			1	
Oxytocin induction				3	3	1
Sum	1	2	1	3	4	1

Table IV 17 *The mean gestational period of children with late-diagnosis CDH (group A) and of children with unstable hips at birth (group B)*

	Boys			Girls			Total		
Group	No.	Mean	S.D.	No.	Mean	S.D	No.	Mean	S.D
A	16	281.37	12.88	26	278.27	14.35	42	279.45	13.73
B	85	286.41	11.61	274	286.10	10.08	359	286.17	10.44

Table IV 18 *The mean birth weight of children with late-diagnosis CDH (group A) and children with unstable hips at birth (group B)*

	Boys			Girls			Total		
Group	No.	Mean	S.D	No.	Mean	S.D	No.	Mean	S.D.
A	16	3 589.69	510.68	28	3 353.93	485.30	44	3 439.66	502.01
B	89	3 684.04	470.70	288	3 605.45	502.55	377	3 624.01	495.73

during infancy (61) These cases may show unilateral restricted abduction and even some shortening of the affected leg, and as X-ray pictures may be difficult to interpret at this early stage unnecessary treatment is often instituted.

The patients of the present series were all examined and treated according to a standardised regime in the Orthopedic Department On the basis of Hospital Records it is difficult to estimate the frequency of possible over diagnosis, but it may be noted that in eighteen patients subluxation or luxation was recorded, making over-diagnosis unlikely in this group

Another factor complicating the comparison of the results of the present study with similar investigations is that most of the published series of the so-called "late-diagnosis CDH" include patients not examined at birth. Results from four counties of southern Norway (12) indicate that the frequency of non-examined cases has decreased from fourty per cent in 1958 to nearly zero in 1966. Similar data are reported from Sweden where the percentage of non-examined cases in 1960 was about thirty and nearly zero in 1963 (60) In many regions the percentage of non-examined new borns is still high (2, 3)

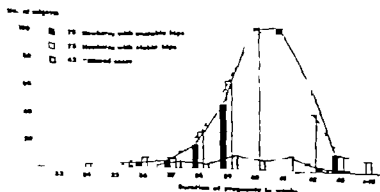


Fig IV 1 The gestational period of children with unstable hips at birth, control newborns and children with stable hips and late-diagnosis CDH ("missed cases").

Table IV 19 *The correlation of birth weight and gestational period in 40 children with stable hips at birth and late-diagnosis CDH*

Weight group	Gestational period <37 weeks	37–41 weeks	>41 weeks	Total
<10 perc.	0	4	0	4 (10 0 %)
10–90 perc.	2	27	2	31 (77.5 %)
>90 perc.	1	4	0	5 (12.2 %)
Total	3 (7.5 %)	35 (87.5 %)	2 (5 %)	40 (100.0 %)

Table IV.21 *The correlation of birth length and gestational period in 40 children with stable hips and late-diagnosis CDH*

Length group	Gestational period <37 weeks	37–41 weeks	>41 weeks	Total
<10 perc.	0	3	1	4 (10.0 %)
10–90 perc.	1	29	1	31 (77.5 %)
>90 perc.	2	3	0	5 (12.5 %)
Total	3 (7.5 %)	35 (87.5 %)	2 (5 0 %)	40 (100.0 %)

Since the pioneer work of Ortolani (58) and Le Damany (41) it has been generally accepted that unstable hips at birth and late-diagnosis CDH represent a common etiological entity Recent investigations (12) seem to indicate that the connection between the two pathological states is far more complicated

At present, it may be generally accepted that in a small proportion of children instability of the hip joint at birth may lead to luxation subluxation or dysplasia, and that bilateral affection breech presentation at birth and affection in girls have a greater tendency to later maldevelopment of the hip (12) Moreover the beneficial effect of abduction splinting against the maldevelopment of the hip seems indisputable (29 60 70)

Coleman (19) suggests that the acetabular index shows diagnostic correlation in only one third of the clinically abnormal hips examined radiologically Caffey (14) could find no support for a congenital dysplasia-predislocation hypothesis of congenital dislocation of the hip based on enlarged acetabular angles limitation of abduction and abnormal skin folds

The results of the present study appear to substantiate the view that unstable hips at birth and late-diagnosis CDH represent separate clinical entities with different etiology and pathogenesis

As can be seen from Table IV.29 the characteristics of the two groups of patients differ in nearly all respects Many of the differences are difficult to explain and need further investigations but even some of the similarities are obscure

In both groups of children there was a high frequency of hip abnormalities in the families of the affected children. The higher incidence of positive family history of the "missed cases was statistically not significant in the present series The results are in agreement with results presented by Bjerkreim (12) who postulates a hereditary basis for "late-diagnosis CDH" up to 95 per cent and for the "neonatal CDH" to 65 per cent.

It has been shown that there are at least two independent genetic mechanisms operating (15 85) One is the development of a shallow acetabular socket and the other a generalised

Table IV.20 *The mean birth length of children with late-diagnosis CDH (group A) and children with unstable hips at birth (group B)*

Group	Boys No.	Mean	S.D	Girls No.	Mean	S.D.	Total No	Mean	S.D.
A	16	51.06	1 34	28	50.00	2.09	44	50.39	1.91
B	89	51.53	1 95	288	50 81	2.07	377	50.98	2.06

Table IV.22. *The mean head circumference of children with late-diagnosis CDH (group A) and children with unstable hips at birth (group B)*

	Boys			Girls			Total		
Group	No.	Mean	S.D	No.	Mean	S.D	No	Mean	S.D
A	15	35.267	1.664	27	34.352	1.486	42	34.679	1.596
B	87	36.155	1.345	286	35.384	1.740	373	35.564	1.687

Table IV.23 *The mean weight of placenta of children with late-diagnosis CDH (group A) and children with unstable hips at birth (group B)*

	Boys			Girls			Total		
Group	No.	Mean	S.D	No	Mean	S.D	No	Mean	S.D.
A	15	634.67	95.38	27	612.59	135.21	42	620.48	121.71
B	86	671.34	131.49	279	676.53	142.22	365	675.30	139.65

Table IV.24 *The ratio of placental weight to foetal weight ('placental coefficient') in children with late-diagnosis CDH (group A) and children with unstable hips at birth (group B)*

	Boys			Girls			Total		
Group	No.	Mean	S.D.	No.	Mean	S.D	No.	Mean	S.D
A	15	0.18	0.02	27	0.18	0.03	42	0.18	0.03
B	87	0.18	0.03	279	0.19	0.03	366	0.19	0.03

Table IV.25 *Pathological placentas of children with late-diagnosis CDH (group A) and unstable hips at birth (group B)*

	Boys		Girls		Total	
Group	No.	%	No	%	No	%
A	1	6.7	5	18.5	6	14.3
B	10	11.6	31	11.1	41	11.2

Table IV.26 *The Apgar score of 42 newborns with late-diagnosis CDH and stable hips at birth*

	Apgar score					
Age of the child (min)	0–4		5–8		9–10	
	No	r	N	%	No	%
1	0	0.0	3	7.4	39	88.6
5	0	0.0	1	2.4	41	93.2
10	0	0.0	1	2.4	41	93.2

joint laxity the first being a polygenic system and the second a dominant trait with incomplete penetrance

In contrast to the "late-diagnosis" CDH cases the instability of the hip joint at birth is very difficult to explain by either of the two mechanisms The transitional character of the instability supports the view that environmental factors are solely or mainly responsible for the condition. The increased frequency of familial incidence of CDH in children with unstable hips may be explained in different ways.

One cannot exclude the possibility that a positive luxation provocation test at birth can only be elicited in cases with a combination of a shallow acetabulum and lax joint capsule. The group of patients with a maldeveloped acetabulum and stable hips will consequently escape diagnosis at birth.

Table IV 19 *The correlation of birth weight and gestational period in 40 children with stable hips at birth and late-diagnosis CDH*

	Gestational period			
Weight group	<37 weeks	37–41 weeks	>41 weeks	Total
<10 perc	0	4	0	4 (10.0%)
10–90 perc.	2	27	2	31 (77.5%)
>90 perc.	1	4	0	5 (12.2%)
Total	3 (7.5%)	35 (87.5%)	2 (5%)	40 (100.0%)

Table IV.21 *The correlation of birth length and gestational period in 40 children with stable hips and late-diagnosis CDH*

	Gestational period			
Length group	<37 weeks	37–41 weeks	>41 weeks	Total
<10 perc.	0	3	1	4 (10.0%)
10–90 perc.	1	29	1	31 (77.5%)
>90 perc.	2	3	0	5 (12.5%)
Total	3 (7.5%)	35 (87.5%)	2 (5.0%)	40 (100.0%)

Since the pioneer work of Ortolani (58) and Le Damany (41) it has been generally accepted that unstable hips at birth and late-diagnosis CDH represent a common etiological entity Recent investigations (12) seem to indicate that the connection between the two pathological states is far more complicated

At present it may be generally accepted that in a small proportion of children instability of the hip joint at birth may lead to luxation subluxation or dysplasia and that bilateral affection breech presentation at birth and affection in girls have a greater tendency to later maldevelopment of the hip (12) Moreover the beneficial effect of abduction splinting against the maldevelopment of the hip seems indisputable (29 60 70)

Coleman (19) suggests that the acetabular index shows diagnostic correlation in only one third of the clinically abnormal hips examined radiologically Caffey (14) could find no support for a congenital dysplasia-predislocation hypothesis of congenital dislocation of the hip based on enlarged acetabular angles limitation of abduction and abnormal skin folds

The results of the present study appear to substantiate the view that unstable hips at birth and late-diagnosis CDH represent separate clinical entities with different etiology and pathogenesis.

As can be seen from Table IV 29 the characteristics of the two groups of patients differ in nearly all respects. Many of the differences are difficult to explain and need further investigations but even some of the similarities are obscure

In both groups of children there was a high frequency of hip abnormalities in the families of the affected children. The higher incidence of positive family history of the missed cases" was statistically not significant in the present series. The results are in agreement with results presented by Bjerkreim (12) who postulates a hereditary basis for "late-diagnosis CDH" up to 95 per cent and for the "neonatal CDH" to 65 per cent.

It has been shown that there are at least two independent genetic mechanisms operating (15 85) One is the development of a shallow acetabular socket and the other a generalised

Table IV 20 *The mean birth length of children with late-diagnosis CDH (group A) and children with unstable hips at birth (group B)*

	Boys			Girls			Total		
Group	No.	Mean	S D	N	Mean	S.D.	No	Mean	S D.
A	16	51 06	1 34	28	50 00	2.09	44	50.39	1.91
B	89	51.53	1 9	288	50.81	2.07	377	50.98	.06

Table IV.29 *Different characteristics of children with late-diagnosis CDH (group A) and children with unstable hips (group B)*

Characteristics	Group A	Group B	Significant difference
Boys/girls ratio	1/1 7	1/3 1	+
Familial occurrence of hip abnormalities	34.1%	23.2%	–
Hypertension in mothers during gestation	22.7%	9.3%	+
Urinary tract infections in mothers	0	10.3%	+
Unspecified infections in mothers	13.6%	0.5%	+
Antiemetics to mothers	0	1.9%	+
Antibiotics to mothers	0	11.9%	+
Birth rank one	40.9%	50.0%	–
Breech presentation	2.3%	16.4%	+
Early liquor efflux	22.7%	10.6%	+
Duration of gestation	279 45 ± 13 73	286.17 ± 10.44	+
Mean birth weight	3 439 66 ±502.01	3 621.59 ±497.30	+
Mean birth length	50.39 ± 1.91	50.97 ± 2.06	+
Mean head circumference	34 679± 1.596	35.564± 1 687	+
Mean weight of placenta	620.48 ±121 71	675.30 ±139.65	+
Irritability	6.8%	1 1%	+
Foot deformities	9 1%	2.4%	+

missed" diagnosis in boys will be difficult to explain.

The relatively low birth weight of children with late-diagnosis CDH has been observed by others (12, 67 69) and is probably a consequence of the relatively short gestational period.

On the basis of the present investigation it may be justified to conclude that the subluxation provocation test is not a completely reliable diagnostic procedure and a careful examination of the hips at regular intervals during infancy seems to be of equal importance

V SUMMARY

Among 19 864 infants born in Trondheim from 1 5 1969 to 31 12 1974 instability of the hip joint was diagnosed in 378 (19 03 per thousand liveborns) There were 93 boys (9 08 per thousand liveborns) and 285 girls (29 61 per thousand liveborns) 103 infants (27 2 %) had instability of the right hip 150 (39 7 %) of the left hip and 125 (33 1 %) displayed a bilateral affection 68 infants (20.2 %) were born by breech presentation 189 infants (50 1 %) were first-born

In part I a detailed analysis of the prenatal and perinatal condition of the newborns with unstable hips was compared with a corresponding analysis of a control group of infants of the same sex and born chronologically next to the infants with unstable hips It could be demonstrated that nearly half of the infants with unstable hips (45 9 %) were born after a prolonged gestational period exceeding 294 days The mean birth weight birth length head circumference and weight of the placenta in girls were significantly higher in the affected group than in the control group Mothers of in- with unstable hips showed complicated deliveries significantly more often than mothers of the control newborns The connection between the prolonged gestational period and instability of the hip joint is discussed

Part II presents an analysis of the 68 infants born by breech presentation. There were 21 boys (30 9 %) and 47 girls (69 1 %) A detailed analysis of the prenatal and perinatal condition of these infants was compared with a corresponding analysis of 262 infants (136 boys and 126 girls) with stable hips born by breech presentation The following characteristics appeared significantly more frequently in children with unstable hips than in the group with stable hips familial occurrence of hip abnormalities female sex birth rank one complications of delivery of the mothers including use of forceps or vacuum extractor and Caesarian section prolonged gestational period increased mean birth weight mean birth length and mean head circumference It is suggested that breech malposition represents only a part of a complex mechanism of pathogenesis and that additional factors are necessary for the production of manifest laxity of the hip joint Among these factors the prolonged gestational period seems to be of great importance Breech malposition may represent only a secondary phenomenon in the most seriously affected infants The breech presentation of twins and the incomplete breech (footling) presentation seem to represent a relatively small risk in the production of unstable hips

In part III the seasonal variation of birth dates of 397 infants (95 boys and 302 girls) with unstable hips at birth born in Trondheim from 1 5 1969 to 1.5 1975 was investigated The birth dates of the affected girls showed a significant seasonal variation with the peak incidence in September and October whereas there was no seasonal peak for the boys The variation of the birth dates of girls showed greater correlation with variations of illumination than with variations of temperature Among 326 256 infants born in Norway from 1 1 1967 to 31 12 1971 a significant seasonal and regional variation in the occurrence of prolonged gestations was demonstrated. Among 315 637 infants born in Norway from 1 1 1970 to 31 12 1974 the mean gestational period of infants born in the winter was significantly shorter than the mean gestational period of infants born in the remaining seasons It is suggested that the seasonal variation of birth dates of infants with unstable hips is due to seasonal variation of the duration of the gestational period and that both light and temperature may have an influence on the duration No seasonal variation of birth dates could

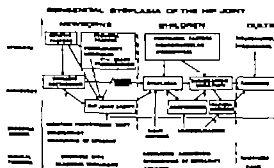


Fig. V.1 The interaction of different factors in the pathogenesis of congenital dislocation of the hip joint.

be demonstrated for infants with birth rank one or for infants born by breech presentation. No seasonal variation of birth dates could be demonstrated for 43 infants with stable hips at birth and late-diagnosis CDH

Part IV deals with 44 children with congenital dislocation of the hip who escaped diagnosis in the neonatal period in spite of examination by the luxation provocation test within two days after birth. There were 16 boys (36 4%) and 28 girls (63 6%). The diagnosis of CDH was made on routine examination in ?0 children by the observation of the parents in 13 and on incidental examination in 7 Radiologically 6 children presented signs of dysplasia and 18 children signs of subluxation or luxation A detailed analysis of the prenatal and perinatal condition of the "missed" cases was compared with a corresponding analysis of 278 children with unstable hips at birth. The characteristics of the children in the two groups differed in nearly all respects, and it is suggested that they represent different etiological and pathogenetical entities. The main characteristics of the "missed" cases was a relatively short mean gestational period (279 45 days ± 13 73 days) and a relatively low mean birth weight (3 439 66 g ± 502.01 g) These characteristics were expressed in girls but not significant in boys It is suggested that the relatively short gestational period is the main reason for the "missed" diagnosis at birth

Results of previous investigations and of the present study indicate that CDH may be caused by a complex interaction of several factors (Fig. V 1)

The *genetic predisposition* operates through *at least three mechanisms, the development of a shallow acetabulum a generalised joint laxity* and the *prolonged gestational period*

Among the *prenatal factors* both *maternal hormones* and *breech malposition* may be of importance but the mode of action of these factors remains obscure

The development of CDH may also be due to *postnatal factors* of both neuromuscular and mechanical origin. The role of these factors as well needs further elucidation.

Congenital dislocation of the hip joint seems *to include several clinical entities with different etiology and pathogenesis. Only further studies can contribute to a more precise definition of the different disorders*

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Juvenile Diabetes Mellitus, Optic Atrophy, Hearing Loss, Diabetes Insipidus, Atonia of the Urinary Tract and Bladder, and Other Abnormalities (Wolfram Syndrome)

A Review of 88 Cases from the Literature with Personal Observations on 3 New Patients

By C. W. R. J. CREMERS, P. G. A. B. WIJDEVELD and A. J. L. G. PINCKERS

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St Radboud Hospital
University of Nijmegen, The Netherlands

JUVENILE DIABETES MELLITUS, OPTIC ATROPHY, HEARING LOSS, DIABETES INSIPIDUS, ATONIA OF THE URINARY TRACT AND BLADDER, AND OTHER ABNORMALITIES (WOLFRAM SYNDROME)

A review of 88 cases from the literature with personal observations on 3 new patients

C W R J Cremers [1] P G A B Wijdeveld[2] and A J L G Pinckers[3]

Department of Otorhinolaryngology, Human Genetics, Internal Medicine Division of Nephrology and Ophthalmology

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INTRODUCTION

Wolfram (78) having been the first to describe the presence of juvenile diabetes mellitus and slowly progressive atrophy of the optic nerve in siblings. Cooper et al. (16) and Wagener (74) pointed out that this syndrome can be associated with diabetes insipidus, atonia and dilatation of the efferent urinary tract and perceptive hearing loss. The last two authors emphasized the autosomal recessive character of this hereditary syndrome.

We had occasion to study three patients with this syndrome, two of whom were siblings. In one of these cases a postmortem was performed after the patient's death. On the basis of our findings in these three patients and a study of 88 cases reported in the literature an attempt will be made to describe the syndrome as carefully as possible. For lack of a designation based on an understanding of the pathophysiology, the syndrome will be referred to for the time being as Wolfram syndrome.

CASE HISTORIES

Patient 1

A woman born in 1946 showed polydipsia as early as age 4. A normal glucose tolerance curve was obtained at that time. At age 8 she showed diminished glucose tolerance but no glucosuria. Diuresis nevertheless amounted to 3–5 l daily, and the maximum specific gravity of the urine after restriction of fluids was only 1008. Endogenous creatinine clearance was not decreased. Intravenous pyelography revealed bilateral hydronephrosis with very marked dilatation of the ureters and an enlarged bladder. Vasopressin seemed to reduce diuresis, but despite use of nasal inhalant powder and a longterm preparation of vasopressin in oil, diuresis continued to vary between [illegible] and 7 l daily. At that time vision was normal, and the ocular fundi showed no abnormalities, the visual fields were intact. A radiograph of the sella turcica revealed no abnormalities. The CSF was found to be normal. The diabetes mellitus was treated by low dosage insulin medication.

We first saw the patient when she was 17 years old. Physical examination revealed that the bladder and both kidneys were palpable as convex resitances. There was typical diabetes mellitus, which was stabilized with the aid of 20–50 U insulin daily. An endogenous creatinine clearance of 34 ml/min indicated unmistakable renal failure. During a 36-hour concentration test, a maximum urinary osmolality of 175 mosmol/kg H_2O was attained, although plasma osmolality rose from 275 to 3[illegible]5 mosmol/kg H_2O. Administration of 700 ml 2.5% NaCl intravenously failed to produce an antidiuretic effect. Intravenous injection of 0.1 U vasopressin led to slight transient antidiuresis with an increase in urinary osmolality from 175 to 225 mosmol/kg H_2O. Intravenous pyelography revealed very marked bilateral hydronephrosis with dilatated ureters. Cystoscopy revealed sclerosis of the bladder neck and a trabeculate bladder. Y–V reconstruction of the bladder neck was carried out, whereupon renal function improved significantly. Endo-

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Key words: diabetes mellitus, optic atrophy, hearing loss, deafness, neurophyseal diabetes insipidus, nephrogenous diabetes insipidus, hydronephrosis, hydroureter, atonic bladder

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Table 1 *The effect of the chlorpropamide on the polyuria in patient 1*

	Diuresis (ml/24 hours)			Urinary osmolality (mosmol/kg H_2O)		
	No. of days	Mean	Range	No. of days	Mean	Range
Untreated	5	6 262	5 350–7 210	5	146	120–170
Ethacrynic acid vasopressin nasal spray	7	4 079	2 945–5 030	7	233	180–280
Chlorpropamide (1 000 mg daily) sodium uptake 10 mmol/day	8	3 165	450–3 650	8	339	280–450
Chlorpropamide (1 000 mg daily) sodium uptake 110 mmol/day	8	3 250	340–5 495	8	376	265–515
Chlorpropamide (750 mg daily) sodium uptake 110 mmol/day	8	3 309	3 070–3 870	8	303	[illegible]55–335

rod adaptation. Colour vision tests indicated an acquired red green disorder in the dichromatic stage

Neurological examinations revealed only a fine nystagmus at age 22 moreover the patient was found to be totally anosmic. Audiometry at age 20 revealed a loss of perception for frequencies exceeding 4 000 Hz. This perceptive hearing loss remained unchanged in subsequent years The patient developed a normal feminine habitus with normal secondary sex characters. A normal menarche occured at age 15 but from age 19 on the patient variously suffered from oligomenorrhoea and amenorrhoea. Gynaecological examination at age 28 revealed as sole abnormality a corpus uteri of insufficient size (probe lenght 3–4 cm normal value 6–7.5 cm)

In 1975 the diabetes insipidus was re-investigated with reference to the possibility of treatment with chlorpropamide. The principal results are shown in Table 1 It was found possible with chlorpropamide to achieve a significant decrease in diuresis and an increase in osmolality to hypertonic values.

Patient 2

We first saw this patient when he was 16 years old He showed a normal level of development with normal secondary sex characters. Physical examination disclosed that the right pupil was wider than the left, the pupillary reaction being slow in both eyes to light, but normal to convergence. Endogenous creatinine clearance was found to have diminished to 8 7 ml/min. During a 24-hour period of fluid restriction the body weight fell by 4 kg, and the plasma sodium concentration rose to 151 mmol/l. Nevertheless the maximum urinary osmolality attained did not exceed 420 mosmol/kg H_2O Administration of 5 U vasopressin tannate in oil during continued fluid restriction led to a maximum urinary osmolality of 505 mosmol/kg H_2O Intravenous administration of 700 ml 2.5% NaCl failed to produce an antidiuretic effect. Intravenous injection of 0 1 U vasopressin caused brief transient antidiuresis with a maximum urinary osmolality of 250 mosmol/kg H_2O Intravenous pyelography (Fig. 3) revealed bilateral hydronephrosis with dilatated ureters. Cystography at micturition failed to reveal vesicoureteral reflux. Cystoscopy showed an enlarged bladder with a small urinary residue. Endoresection was performed.

Neurological examination revealed no abnormalities. Ophthalmological examination showed reduced visual acuity· VODS=3/10. The visual fields showed concentric limitation. Atrophic discs were seen in the fundi. There was vasoconstriction. No haemorrhages or exudates were observed.

The patient died from urosepsis after the endoresection. The postmortem disclosed marked dilatation of the renal pelves ureters and bladder There was slight trabeculation in

Fig 3 An IVP in case 2 at age 16.

the bladder wall The hypophysis was normal as were the hypothalamus thalamus substantia nigra and red nucleus The optic nerves optic chiasm and both optic tracts showed slight gliosis and a loss of myelin structure but no signs of active demyelination.

Patients 1 and 2 are siblings (the fifth and sixth child in this family respectively) The third child (a girl) died at age 4 The remaining three children are in good health Their parents are consanguineous (Fig 4) A maternal uncle (meanwhile deceased) had undergone nephrectomy A paternal aunt was recently diagnosed to suffer from diabetes mellitus.

Patient 3

A woman born in 1956 showed polyuria, polydipsia and polyphagia at age 5 Diab mellitus was diagnosed and treated with

lin At that time diuresis already proved to amount to 3–5 l daily without glucosuria In the course of subsequent years this polyuria increased to a diuresis level of 6–12 l daily It proved possible to control the polyuria by daily administration of 5 U vasopressin tannate in oil. When the patient was 19 years old we had occasion to analyse the polyuria. Endogenous creatinine clearance at that time was 100 ml/min Intravenous pyelography revealed normal kidneys with only slightly dilatated ureters and a large bladder (Fig. 5) Within a few days of discontinuation of the vasopressin tannate diuresis increased from 1 5 to 11 l/24 hours while urinary osmolality decreased from 400–550 to 80 mosmol/kg H_2O Intravenous administration of 700 ml 2 5% NaCl failed to produce an antidiuretic effect nor did 0 1 U vasopressin intravenously lead to antidiuresis. This patient too proved to respond well to chlorpropamide diuresis decreased to values between 750 and 1300 ml/24 hours with a urinary osmolality of about 500 mosmol/kg H_2O Radiological examination of the sella turcica showed no abnormality

In this case visual disorders developed at an early age visual acuities being: VODS=2/10 at age 8 1/10 at age 10· VOD=1/30 VOS 1/100 at age 11 VOD=1/60 VOS=1/300 at



Fig 5 An IVP in case 3 at age 19

age 17 At age 8 the discs were pale, and at age 10 they were atrophic. At age 11 the visual fields showed peripheral concentric limitation, a large centrocoecal scotoma was observed At age 17 the lenses showed very delicate subcapsular clouding. There were no signs of diabetic retinopathy Split-lamp examination showed a delayed pupillary reaction to direct as well as to indirect light. The ERG was normal in both eyes The dark adaptation curve was slightly disturbed Retinal function therefore was largely intact. The pathology was localized for the most part at the level of the optic nerve but not at the retinal level Fluorescence angiography revealed marked disc atrophy There were virtually no signs of diabetic retinopathy or macular lesions.

At age 12 the patient developed neuritis of the left peroneal nerve, and recurrent neuralgia in the area of the mandibular nerve developed after age 13 Electromyographic and electroneurological studies at age 19 indicated distal polyneuropathy motor as well as sensory without signs of active denervation The CSF was normal. The EEG was indicative of an increased tendency towards epileptic activity Pneumoencephalography revealed no abnormalities.

Audiometry disclosed bilateral perceptive hearing loss of 40–50 dB in the range from 250 to 2000 Hz and 75–80 dB in the range from 4000 to 8000 Hz. There were no gynaecological disorders. The patient s secondary sex characters were normal for her age. Menarche at age 16 with subsequently a regular menstrual cycle. The aminoacid chromatogram of the urine was undisturbed

The patient was the youngest of three children. Her mentally subnormal elder sister died at age 7 her 25-year-old brother was in good health. There was no evidence of a familial occurrence of symptoms of this syndrome. Genealogical studies through five generations failed to produce indications of consanguinity

THE WOLFRAM SYNDROME IN THE LITERATURE

We traced 100 cases of this syndrome in the literature (4 8 10 13 15 18 20 1 24 28 31 33 35 37 40 44 49 54 55 57 60 62, 63 65 66, 67 68 69 71 72 73 78) Ten case reports (3 14 —, 29 30 43) were unsuitable for analysis and two (9 17) were traced too late for inclusion in this study The frequency of symptoms in these cases is shown in Table — Most of these symptoms will be discussed separately

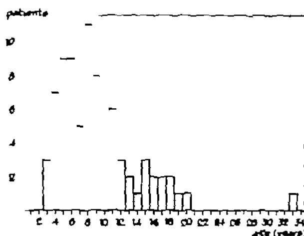


Fig 6 Age at which diabetes mellitus was diagnosed in 83 patients.

Juvenile diabetes mellitus

The age at which diabetes mellitus was diagnosed in 83 of these cases is indicated in Fig. 6. Diabetes mellitus was the first symptom in 76% of cases A striking finding was that some siblings of patients with this syndrome died as a result of a diabetic coma.

Ophthalmological findings

e age at which reduced visual acuity was gnosed in 88 of these cases is shown in ig. 7 The decrease in visual acuity was progressive and as the reports indicate repeatedly led to blindness In all cases showing decreased visual acuity fundoscopy revealed optic atrophy (unless cataract precluded this) The optic atrophy was characterized by pale sharply defined optic discs. Not all case reports made mention of limitation of visual fields this was usually due to the fact that vision was already so reduced that it was difficult to determine the visual fields. Concentric limitation of the peripheral visual field was nearly always progressive A central or centrocoecal scotoma was only rarely observed More or less pronounced bilateral cataract was described in 9 patients (8 15 18 28 33 60 73) A unilateral cataract was described by Shaw & Duncan (65) The descriptions are too brief and superficial for more exact definition of the type of cataract involved.

Stansbury (66) was the first to report disturbed colour vision in two patients Rorsmann & Söderström (60) Cordier et al (18) and Stevens & Macfadyen (67) specified an acquired red–green disorder This is consistent with the fact that a non-autosomal dominant optic atrophy is associated with an acquired red–green disorder (type II Verriest) as described by François & Verriest (25 26) and Pinckers (56)

Stansbury (66) reported that his first (female) patient had better night vision than day vision Rorsmann & Söderström (60) Niemeyer & Marquardt (55) and Laffay & Lestradet (44) reported on dark adaption in a total of 5 patients

Some authors (15 33 54 60) described some pigment scatter in the central as well as

Table 2 *Percentage of symptoms in 88 patients with the Wolfram syndrome*

	Yes	No	Not specified
Diabetes mellitus	99	1	–
Visual disorder	98	2	–
Optic atrophy	98	2	–
Changes in visual fields	39	11	50
Disturbed colour vision	27	–	73
Retinal pigmentation	9	33	58
Hemeralopia	6	–	94
Cataract	10	1	89
Slow pupillary reaction to photic stimuli and/or convergence	18	7	75
Nystagmus	13	25	63
Abnormal audiogram	39	20	41
Reduced excitability vestibular apparatus	6	2	92
Diabetes insipidus	32	30	39
Hydronephrosis	15	23	63
Hydroureters	11	5	84
Atonic neurogenous bladder	13	5	83
Sclerosis bladder neck	1	5	94
Local dilatation of colon	1	–	99
Disturbed coordination and/or ataxia	7	–	93
Disturbed EEG	16	25	59
Increased CSF protein	1	10	89
Undisturbed aminoacid chromatogram of urine	14	–	86
Daily amount of amino-aciduria know	2	–	98
Hyperalaninuria	2	–	98

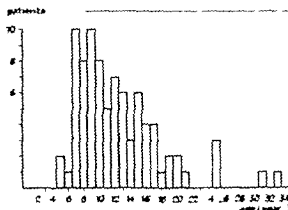


Fig. 7. Age at which diminished visual acuity was diagnosed in 88 patients.

the peripheral retina. These pigmentations showed no typical features. The retinal vessels are usually intact. Only rarely are they constricted or abnormally tortuous. Microaneurysms may be present, but signs of a diabetic retinopathy are usually absent.

ERG findings were reported for a total of 19 patients (8, 15, 4, 28, 44, 55, 63, 73). Niemeyer & Marquardt (55) observed only slight ERG changes and, also in view of the overall clinical ophthalmological features, concluded that the visual disorder was mainly due to a lesion in the ganglion cell layer and the nerve fibre layer. So far as the outer retinal layers are involved in the process, it is chiefly the cone system that is affected. Our observations corroborate Niemeyer's conclusion.

Enlarged pupils (unusual diameter 4–7 mm) were described in 16 patients (4, 10, 15, 21, 28, 55, 6., 63, 66). The pupils were round and showed only a feeble response to a strong photic stimulus and to convergence.

Hearing loss

An audiometric examination was mentioned in 5 of the 88 cases: the audiogram was abnormal in 34, while subjective complaints were mentioned in only 12 cases. Three of these patients attended a school for the deaf. Fig. 8 shows the age at which hearing loss was diagnosed in 28 patients. There is a remarkably even distribution over the first 30 years of life. The hearing loss mostly involved the high frequencies and, if progressive, extended to the high as well as to the low frequencies. Progression was as much more marked as the hearing loss occurred at an earlier age. A progressive course can cover a period as long as 10 years. Although diabetes mellitus is known in the long run to be associated with hearing loss (38), this does not seem to explain the hearing loss in these cases, which occurred at a very early age.

Barjon et al. (7), Demailley et al. (1) and Laffay & Lestradet (44) each described one patient with recruitment. Herrera Pombo et al. (33), Demailley et al. (21) and Laffay & Lestradet (44) each specified absence of recruitment in one patient.

Vestibular apparatus

Examination of the vestibular apparatus was mentioned in only 7 patients. Barjon et al. (7, 8), Klinger et al. (40) and Goddon et al. (28) described reduced *excitability of the vestibular apparatus* in a total of 5 patients, one of whom showed a normal audiogram. Grosz & Berki (31) and De Sanctis et al. (62) mentioned undisturbed vestibular excitability in patients with a normal audiogram. Laffay & Lestradet (44) concluded from a nystagmographic study of 1 patient that the reduced excitability of the vestibular apparatus was of central origin.

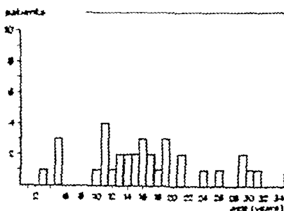


Fig. 8. Age at which hearing loss was diagnosed in 34 patients.

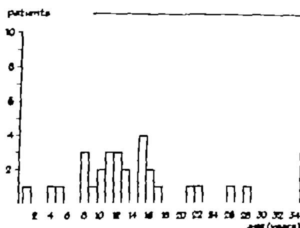


Fig 9 Age at which diabetes insipidus was diagnosed in 28 patients.

Diabetes insipidus

Diabetes insipidus was diagnosed in 28 of the 88 patients described (10 13 20 28 33 35 37 40 44 49 54 57 62 68 69 73) For 26 patients it was explicitly mentioned that no diabetes insipidus existed and in 34 patients no mention was made of polyuria or polydipsia. Fig. 9 indicates the age at which diabetes insipidus was diagnosed in 28 patients the range was 3–21 years The diagnosis was based on a polyuria of 4–12 l daily with specific gravities between 1 000 and 1 005 In all cases the polyuria could be partly or entirely controlled by vasopressin administration. Only in a few patients however was a maximum specific gravity of 1 020 attained during vasopressin medication (35 62) the maximum specific gravity usually attained was 1 008–1 015 The polyuric patients often showed dilatation of the efferent urinary tract: hydronephrosis hydroureter atonic bladder Of the patient who attained a normal specific gravity of urine during vasopressin medication, one showed no abnormalities of the efferent urinary tract (35) and one showed severe hydronephrosis with dilatated ureters and an enlarged bladder (62) Reliable data on renal function in these patients are very scanty Endogenous creatinine clearance was sometimes normal (57 33) but in other cases decreased to 60–65 ml/min (57 62)

The antidiuretic effect of the antihypoglycaemic sulphonyl-urea derivative chlorpropamide which is believed to be confined to the neurohypophyseal form of diabetes insipidus with still a small residual vasopressin production (46 48) and to be based on potentiation of the effect of submaximal vasopressin levels on the tubular system (36 46 47 48) was quite manifest in 5 patients (37 44) whereas in 2 patients (28 44) it was reported not to have been effective

Dilatation of the efferent urinary tract

Some patients had an atonic neurogenic bladder Cooper et al. (16) and Wagener (74) subsequently mentioned this for 2 of the 4 patients previously described by Wolfram (78) Shaw & Duncan (65) reported a strikingly dilatated bladder in one patient, as did Niemeyer & Marquardt (55) Raiti et al (57) described hypertrophy of the bladder in one patient Bretz et al. (10) described a patient with an atonic enlarged bladder with a residual volume. Cysto-ureterography disclosed no reflux In a second patient he found a hypertrophic atonic bladder An enlarged bladder was also described by Moore (49) De Sanctis et al (62) Goddon et al. (28) and Laffay & Lestradet (44) Mention was made of a normal bladder by Raiti et al. (57) Ikkos et al. (35) and Laffay & Lestradet (44) Niemeyer & Marquardt (55) noted that his second patient had undergone Y–V reconstruction of the bladder according to Young because of sclerosis of the bladder neck. This was likewise observed in our first two patients Sclerosis of the bladder neck was described as absent in 4 patients with diabetes insipidus by Raiti et al (57) De Sanctis et al. (62) and Laffay & Lestradet (44) In the other case reports the subject was not mentioned.

Neurological changes

So far the literature has made no mention of olfactory disorders and the anosmia in our third patient is therefore remarkable

Reduced or absent tendon reflexes were frequently mentioned Sauer et al. (63) reported cerebellar ataxia in his second patient, indicative of slight damage to the pyramidal tract. In his first patient he noted conspicuous uncertainty in the fingertip–fingertip test and in walking a straight line Clifford Rose et al (15) described features reminiscent of Friedreich s ataxia in his sixth patient The first patient described by Tunbridge & Paley (71) complained about a swaying gait but neurological examination revealed no abnormalities One of Wolfram s patients was subsequently described as showing ataxia Van Ussel & Hoet (73) noted an uncertain gait in one patient, as did Laffay & Lestradet (44) Electromyographic and electroneurological examination revealed a reduced proprioceptive and motor conduction velocity The fourth patient described by Laffay & Lestradet (44) presented a clinical impression of muscular weakness Muscular tonus and strength sensitivity and motor conduction velocity were normal but electromyographic findings were indicative of a disturbance

EEG changes were reported in 14 patients (10 15 33 37 40 44 55 63 69) The EEG was reported normal in 22 patients and 52 reports made no mention of EEG findings Tyrer (72) and Bretz et al (10) each described two patients with epilepsy

The CSF protein concentration was normal in 9 patients (10 71 28 54 57 63 73) Only Clifford Rose et al. (15) reported an abnormal value (103 mg/100 ml) in one patient.

Sexual maturation

Sexual maturation seemed retarded in a number of patients. Mention was frequently made of menstrual disorders sometimes leading to amenorrhoea. Secondary sex characters were not always at a level of development consistent with chronological age This was illustrated by the first patient described by Ikkos et al (35) clinical examination showed a well-proportioned small woman with a normal height–weight ratio She looked much younger than her calendar age. Mammary development and hairgrowth pattern were normal but the external genital organs and uterus were unmistakably atrophic At age 20 she still awaited the menarche. Vaginal smears showed slight-to-moderate oestrogenic activity without any significant variation in the course of a month

Cordier et al (18) mentioned a patient who had three pregnancies invariably ending in stillbirth in the 8th month. Laffay & Lestradet (44) described a boy who presented the appearance of a Klinefelter syndrome He had a normal karyotype. There was gynaecomastia (diameter 5 cm) with an areola of 3 cm diameter Demailley et al (21) reported that a testicular biopsy specimen from this boy showed the features of gonadal atrophy

Laboratory findings

Aminoacid chromatography of the urine revealed no abnormality in 12 patients. Ikkos et al (35) reported that the daily aminoaciduria in one patient (600 mg/24 hours) was 4 times as high as the upper limit of normal. Niemeyer & Marquardt (55) described hyperalaninuria in two patients.

Heredity

There are sound reasons to assume that the hereditary transmission of this syndrome is autosomal recessive

1) the male female ration in 86 patients was 45 41

2) the literature comprises 57 families in 12 of these families parental consanguinity was demonstrated (15 24 28, 33 35 44 54 69 77)

3) the syndrome also occurs in siblings not in parents and only rarely in cousins

4) in 38 of the 57 families the family composition and health of the siblings were sufficiently known for segregation analysis in addition to the 38 probands there were 33 siblings with this syndrome There were 92 healthy siblings and 6 siblings (alive or dead) with this syndrome The ratio between af

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Author address

Department of Otorhinolaryngology
St. Radbout Hospital
University of Nijmegen
The Netherlands

TO ARCHIATER, DR ARVO YLPPÖ
ON HIS 90th ANNIVERSARY
27 10 1977

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SUPPLEMENT 265, 1977

From the Department of Paediatrics (Head. Professor Tuomas Peltonen, M.D.)
University of Turku, Turku, Finland

SOCIAL AND MEDICAL PROGNOSIS OF CHILD WITH ACUTE NONTUBERCULOUS PURULENT MENINGITIS

by

MATTI SILLANPÄÄ TUOMAS PELTONEN and TURO NURMIKKO

TURKU 1977

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INTRODUCTION

The antimicrobial therapy of bacterial diseases has radically altered the entire character of paediatrics during the past two decades. Child mortality due to infectious diseases has decreased to a fraction of its past level. Some bacterial infections such as cholera, leprosy diphtheria and in great part tuberculosis have been succesfully eliminated in the Scandinavian countries by means of improved hygiene and social medicine. Efficient antibiotics and other chemotherapeutic agents have been developed to combat bacteria and many other microorganisms Some bacteria have been found to undergo changes in pathogenicity without any medical intervention; cases in point are e.g. scarlet fever (38) and meningococcus (36)

Bacterial meningitis is still a dangerous disease even though theoretically the organism causing this disease can be destroyed by means of antimicrobial therapy The often unpredictable course of the disease arises from damage to or total destruction of the vital centres of the central nervous system rather than from the pathogen itself On the other hand the central nervous system is physiologically well protected against foreign substances carried by the blood. This characteristic is however a handicap in terms of treatment, since it reduces the possibilities of antibiotic therapy Many antibiotics are unable to enter the CSF to any extent which would be of therapeutic value under normal conditions. Decisions concerning antibiotic administration should therefore be mad after careful consideration. On the other hand, even the time required for an aetiologic diagnosis and the determination of the susceptibility of the bacteria to antibiotics may represent a fatal delay in the treatment of a patient with meningitis. The paucity of pathognomonic symptoms of meningitis in neonates and young infants also tends to cause delay All these factors contribute to the persistence of a certain level of lethality in bacterial meningitis. Since furthermore bacterial meningitis may result in mental retardation as well as neurologic and orthopedic sequelae the disease represents an essential problem of social paediatrics.

PURPOSE OF THE PRESENT STUDY

The economic region of Turku is among the most prosperous areas of Finland; it has good road connections to the Paediatric Department of the University of Turku and the nearest specialist-directed paediatric hospital is within a distance of less than 50 km from any point. Practically all paediatric cases of bacterial meningitis have ultimately been transferred to our department for treatment. Our objective in this study is to examine the medical prognosis of these patients and the factors which affect it, together with the patients' social educational and occupational prognosis. The study sample consists of all the children treated for meningitis during the years 1948—1972. The year 1948 was chosen as the initial point of the study because by that time all the post war regulations concerning the rationing of food and fuel had been abolished while at the same time all the antibiotics which are still today essential to the treatment of purulent meningitis were in principle already available

SUBJECTS AND METHODS

The records consisted originally of 297 meningitis patients; 44 of them however had tuberculous meningitis and were therefore excluded from the study since tuberculosis as the causative agent in meningitis disappeared in our catchment area in the beginning of the 1950's (in 1952 and 1954 there was one sporadic case of tuberculous meningitis each year) In the case of 9 patients the data were insufficient or no data could be obtained; thus they also had to be excluded. The remaining 244 patients were *included in the study and information* concerning their subsequent life histories was gathered. Of these 244 152 were males and 92 females. All these patients received medical treatment from at least one of the present authors (M.S. or T.P.) The average length of the follow-up period in those who survived is 12 years (the shortest being 2 years and the longest 25 years) Similarly the age of the subject at the end of the follow-up period varied from 4 to 40 years with the mode around 20 years (Fig. 1) Besides the medical records of our own department, we have had at our disposal the records of the treatment units in which the subjects have received medical care. Further information has been obtained by interviewing the subjects and their relatives as well as teachers and employers where necessary In addition, data have been obtained from mortality statistics. Approximately a third of the subjects of the present sample still come to our outpatient department for a regular annual check-up.

In the age classification we have employed the system used in English speaking countries neonates 0—28 days, infants 1 month—2 years children more than 2 years. The occupational classification is based on Rauhala's analysis (27 28) of the social and occupational stratification of Finnish society

The basic principle of drug therapy throughout the patient series was as follows cases with H. influenzae or negative CSF stain were treated with chloramphenicol whil*e all other cases received a combi*nation of sodium penicillin and sulfonamides until the CSF culture results with the antibiogram were available. The initial antibiotic therapy in neonates was the combination of penicillin and one of the aminoglycerides.

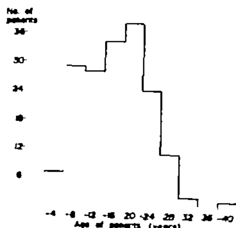


Fig. 1. Age of the patients at the ... of the follow-up ...

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Table 3. *Day time caretaker of patients and age at onset of purulent meningitis*

Caretaker	Neonates	Infants	Children	Total
Own mother	8 (5 %)	9 (62 %)	49 (33 %)	148 (100 %)
Other family member	(17 %)	4 (66 %)	1 (17 %)	6 (100 %)
Household help		6 (67 %)	3 (33 %)	9 (100 %)
Full-time day nursery	0	0 (77)	3 (23 %)	3 (00)
Other	28 (65 %)	10 (23 %)	5 (12)	43 (100 %)
Total	37 (17 %)	12 (55 %)	6 (28 %)	2 9 (00 %)

ferred from hospitals for the treatment of chronic illnesses institutions for the handi capped or children s institutions. The ot hers came from their own homes.

A total of 30 % of the patients were born in the University Hospital and 22 % in a separate local maternity hospital (Table 4) A third of the subjects had been born in a local or district hospital and 6 % in a coun ty hospital. Home delivery had taken place in 8 % of the cases. The place of birth was not statistically significant for neonates with meningitis although the proportion of those born in county hospitals was lowest. Table 5 shows that cases of meningi tis and thus also childbirths tend to con

Table   *Plac of birth and age t onset of purule t meningitis*

Place of birth	Neonates	Infants and children	Total
University hospital	(7 %)	55 (83 %)	66 (00 %)
County hospital	(8 %)	12 (92 %)	3 (100 %)
Separate maternity hospital	7 (14 %)	43 (86 %)	5 (100 %)
Local hospital	4 (8 %)	62 (82 %)	76 (100 %)
Home birth	3 (17 %)	5 (83 %)	8 (00 %)
Total	36 (6 %)	87 (84 %)	223 (100 %)

T ble 5 *Plac of birth according to yea of bi h*

Place of birth	Year of birth			Total
	Before 953	953—6	963—72	
University hospital	4 (%)	(7 %)	31 (35 %)	67 (28 %)
County hospital	3 (7 %)	3 (3 %)	14 (6 %)	20 (8 %)
Separate maternity hospital	6 (42 %)	30 (6 %)	17 (9 %)	63 (26 %)
District or local hospital	5 (3 %)	(37 %)	7 (30 %)	76 (3 %)
Home birth	0 (7 %)	3 (7 %)		8 (7 %)
Total	38 (00 %)	1 7 (00 %)	89 (00 %)	244 (00 %)

centrate more than before in central or county hospitals and that since the 1960's home births no longer occur among menin gitis patients.

Age at onset The age of the subject at the onset of meningitis is shown in Table 6 The disease is most frequent in the latter part of infancy with 62 cases (25 %) The neonates are second, with 38 cases (16 %) If however the incidence frequency is il

Table 6. *Age at onset of purulent meningitis*

Age	Age distribution of patients Number of patients
0—28 days	38 (16 %)
29 days—3 months	31 (13 %)
4—6 months	24 (0 %)
7—12 months	37 (15 %)
13 months—2 years	61 (25 %)
3—7 years	35 (14 %)
8—15 years	17 (7 %)
Total	244 (100 %)



Fig 3 Proportional risk for purulent meningitis in different paediatric age groups

lustrated graphically in relation to time the graph shown in Fig. 3 is obtained in which the number of neonatal cases is designated by 100. A total of 54 % of the patients had contracted the disease during the first year of life.

Infectious agents Meningitis caused by H. influenzae is most common in infants whereas cases caused by meningococcus and pneumococcus are evenly distributed among infants and children (Table 7) All cases of meningitis caused by E. coli occur in either the neonatal period or in early infancy In the category of other known

Table 7 *Infectious agents in different age groups*

Infectious agent	Age groups			
	Neonates	Infants	Children	Total
H. influenzae	1 (%)	53 (69 %)	23 (30 %)	77 (100 %)
Meningococcus	0	15 (52 %)	14 (48 %)	29 (100 %)
Pneumococcus	2 (5 %)	20 (51 %)	17 (44 %)	39 (100 %)
E. coli	16 (76 %)	5 (24 %)	0	21 (100 %)
Other known	9 (26 %)	18 (51 %)	8 (23 %)	35 (100 %)
Sterile purulent	2 (6 %)	21 (62 %)	11 (32 %)	34 (100 %)
Total	30 (13 %)	132 (56 %)	73 (31 %)	235 (100 %)

the most common bacteria are St. albus (6 cases) and aureus (5) streptococcus (5) and a gram positive coccus not further defined (4) They are fairly evenly distributed among the different subject groups. Those cases which were first treated as a disease other than meningitis occurred mostly either in the neonatal period or in infancy

Symptoms of respiratory infection were manifested prior to the onset of purulent meningitis by 84 patients (35 %) and symptoms of other infection by 23 cases (9 %)

Pre-existent illness Five patients had spina bifida cystica and 11 patients operated hydrocephalus. In addition 23 patients had some other disease with a predisposition to meningitis such as infection in the perinatal period, diabetes or cranial fistula.

Treatment seeking. Since most of those who contracted the disease in the neonatal period (71 %) were still in a maternity ward or maternity hospital at the onset of the illness they were transferred either to the paediatric ward of that hospital and thence to the Paediatric Department of the University of Turku or directly to this department. Of those who contracted meningi-

tis after the neonatal period more than half (52 %) sought treatment first from the district medical officer of health or a pri vate practitioner and a third (33 /•) sought treatment directly from the Paediatric De partment of the University of Turku. The remaining 15 •/• sought help first in the outpatient departments of other hospitals. The first physician in charge of the case was a paediatrician in two thirds of the cases (67 /•) and a general practitioner or a specialist other than a paediatrician in the remaining 33 •/•

Previous antibiotic therapy Nearly one half (46 •/•) of those who contracted the disease after the neonatal period had recei ved antibiotic therapy before admittance to the Paediatric Department of the Uni versity of Turku. The duration of this the rapy was less than 24 hours in 30 /• ot pre treated cases 2—3 days in 36 % and longer than 3 days in 34 /• of cases.

Duration of meningitic symptoms prior to the initiation of antibiotic therapy was 0—24 hours in 60 /o 2—3 days in 30 % and longer than 3 days in 9 • of the subjects.

Bacteriological diagnosis of meningitis. Both the bacterial stains and cultures were positive in approximately three fourths (7 /•) of the cases. In all three age groups the total CSF leukocyte count was more than 5000 mm³ in 46 % of subjects 1000—5000 mm³ in 33 % and 100—1000 mm³ in 11 % of subjects. In only 5 % of the neonatal ca ses was the CSF leukocyte count under 100. These were cases which had previously re ceived antibiotic therapy for some days. As for CSF granulocytes the proportions were 83 % for neonates 89 % for infants and 94 /• for children.

The total CSF protein level was clearly higher in the neonates than in the other groups ranging from 100 to 2000 mg% in 86 /o of the neonates and in 74 % of the infants and children. The CSF sugar level was 25 mg% or less in 74 % and 26—50 mg% in 26 •/ of the neonates. The corres ponding figures for the infants were 61 /o and 22 %. After infancy the decrease in the CSF sugar values was not as marked as in dicated by the fact that levels of 0—25 mg% occurred in 52 /• of the older subjects and levels of 26—50 mg% in 16 %.

Recovery Table 8 shows the normalisa tion of the CSF values in the course of anti biotic therapy With respect to both bacte rial staining and cultures normalisation

Table 8 *Normalisation f CSF values during antimicrobial therapy*

Criteria	Normalisation (days)						
	0—	2—5	6—10	—15	6—20	20	Total
Bacterial stain	67 /	5	4		1	2 %	100
Bacterial culture	74	9 /	3		1	2	00
Total leukocytes				4	5	58 %	00
Total proteins	6	6	22	18	14	24	
Total glucose	3	24	7	13	4	11	00

usually took place in a few days whereas in the case of total leukocyte count and total protein values it usually took 2 to 3 weeks.

Clinical recovery was attained most ra pidly in the case of meningococcic menin gitis (Table 9) inasmuch as nearly one third (30 %) of those who had contracted this form of meningeal infection were free of symptoms within 0—14 days from the on set of illness. The slowest recovery occurred in the case of meningitis caused by E. coli,

Table 9. *Recovery from clinical signs of purulent meningitis related to infectious agent*

Infectious agent	Recovery after the period of 0—14 days	15—30 days	31—100 days	Total
H. influenzae	16 (22 %)	45 (63 %)	11 (15 %)	72 (100 %)
Meningococcus	8 (30 %)	5 (59 %)	3 (11 %)	27 (100 %)
Pneumococcus	5 (19 %)	11 (70 %)	3 (11 %)	27 (100 %)
E. coli	0	6 (75 %)	2 (25 %)	8 (100 %)
Other known	2 (10 %)	11 (55 %)	7 (35 %)	20 (100 %)
Sterile purulent	9 (28 %)	19 (59 %)	4 (13 %)	32 (100 %)
Total	40 (22 %)	113 (61 %)	30 (17 %)	186 (100 %)

Table 10. *Lethality of purulent meningitis related to different infectious agent*

Infectious agent	Survived	Dead	Total
H. influenzae	71 (92 %)	6 (8 %)	77 (100 %)
Meningococcus	28 (90 %)	3 (10 %)	31 (100 %)
Pneumococcus	25 (64 %)	14 (36 %)	39 (100 %)
E. coli	6 (27 %)	16 (73)	22 (100 %)
Other known	17 (43 %)	23 (57 %)	40 (100 %)
Sterile purulent	31 (89 %)	4 (11 %)	35 (100 %)
Total	178 (73 %)	66 (27 %)	244 (100 %)

all of these patients displayed symptoms longer than two weeks. The average duration of symptoms was 0—2 weeks in 22 % of the sample 0—14 days in 22 % 15—30 days in 61 % and 31—100 days in 17 % of the sample.

Lethality The total number of deaths was 66 (27 %) of whom 61 patients (25 %) died in the acute phase of the disease. In *56 of these the cause of death was meningitis accounting for 85 % of the total number of deaths.* Complications of meningitis caused the death of 8 subjects (12 %) of whom six had hydrocephalus one a cerebral abscess and one sagittal sinus thrombosis Two deaths were entirely unrelated to meningitis one by suffocation in a sand pit and one (a suicide) by shooting.

A major factor in lethality was a preexistent illness predisposing to meningitis. All the patients affected with spina bifida cystica died as did one half of the shunt operated hydrocephalus cases Two thirds of those who had been affected with some other condition predisposing to meningitis died during the follow up period. Lethality was in the cases involving a predisposing disease at a very highly significant level ($p<0.0005$) higher than in the others.

An acute lethality of cases without any pre-existent predisposing illness was 18 %.

The effect on the prognosis of the infectious agent on the one hand and the age of *the patient on the other is difficult to determine since certain types of meningitis tend* to go with certain age periods. Table 10 summarizes the lethality of the entire sample according to infectious agent. It appears that only 8 % of the patients with H. influenzae meningitis and 10 % of those with meningococcic meningitis died compared to 73 % in the case of E. coli infections. Lethality due to pneumococcus was 36 %.

A total of 39 % of the cases (36 patients) died during the neonatal period. One-half of these had E. coli infections. The proportion of premature infants was 24 % of the

cases with neonatal meningitis and 36 % of those who died. In infancy pneumococcus and H. influenzae were the most frequent organisms causing death.

The duration of illness prior to the final and correct diagnosis followed by appropriate treatment, seems to be a more important factor in affecting lethality than the causative organism with an increase in the duration of symptoms prior to the correct diagnosis to 0—15 days the incidence of lethality increases from 19 % to 56 %. The difference is nearly significant ($p<0.05$) In terms of the social background of the mother or the father no statistically significant factor influencing the prognosis of lethality was found in the present study Likewise the mother's work outside the home the patient's place of day care the place of domicile and the distance from the home to the Paediatric Department were nonsignificant.

Medical prognosis

Meningitis resulted in permanent disability in 44 patients (24 %) This disability took the form e.g. of changes in psychic functioning (19 %) mental retardation (18 %) motor disability (15 %) hydrocephalus (11 %) sensory defects (9 %) and epileptic fits (8 %) Two thirds of the subjects had at least two types of disabilities and 15 % had three or more. In the following, the prognosis is considered in terms of age at onset, infectious agent and the patient's social background.

Psychomotor prognosis Table 11 shows the breakdown of the survivors of the entire sample into healthy the mildly disabled and the severely disabled at the time of the follow up examination. Among those mildly or moderately disabled the largest group consisted of those who had been infected with H influenzae; these accounted for 38 % of the mildly or moderately disabled double the proportion of pneumococcus patients and six times the number of cases with meningococcic meningitis. In the severely disabled group the most frequent infectious agent was again H. influenzae (33 %) whereas in the case of pneumococcus and meningococcus no subject was left with severely disabling effects. Neonatal meningitis caused by E. coli resulted in severe disablity in 17 % of cases.

From an examination of sequelae in terms of infectious agent it appears that E. coli is the organism most frequently causing disablity (38 %) H. influenzae is second to it among the individual bacteria (23 %) and pneumococcus ranks third.

Social status, as determined on the basis of the parent's or guardian's occupation was not related to the degree of disability

Table 11 Psychomotor outcome after purulent meningitis related to infectious agent

Infectious agent	Psychomotor handicap						Total	
	No		Mild-moderate		Severe			
H influenzae	55	(77 %)		(17 %)	4	(6 %)	71	(100 %)
Meningococcus	5	(93 %)		(7 %)			7	(100 %)
Pneumococcus		(78 %)		(22 %)	0		7	(100 %)
E. coli	5	(62 %)		(3 %)		(25 %)	8	(00 %)
Other known	9	(48 %)	5	(26 %)	5	(26 %)	19	(100 %)
Sterile purulent	24	(78 %)	6	(9 %)		(3 %)	3	(00 %)
Total	39	(76 %)	32	(7 %)	12	(7 %)	83	(00 %)

A total of 90 % of those completely healthy fell into the five lowest social strata out of nine. In the two middle strata were 69 % of the normal, 74 % of the mildly or moderately disabled and 100 % of the severely disabled patients.

Mental prognosis Intellectual functioning was completely normal (IQ>85) in 150 patients (82 %) (Table 12) 17 cases (9 %) were classified into the mentally subnormal category Seven of these also had a motor handicap one was afflicted with hydrocephalus and two with epilepsy Only four of the subjects had mild or moderate *mental retardation* while 12 patients had severe or profound retardation. Comparing the mental level of the patient with that existing prior to the outbreak of purulent meningitis it appears that eight patients had been mentally subnormal already before infection, while two had been mildly and one moderately retarded. After meningitis there was evidence of further mental retardation in two subnormal patients one being classified as mildly and the other moderately retarded. Two patients who were initially mildly retarded remained at the same level after recovery from purulent meningitis.

Motor functioning was completely normal after meningitis in 156 patients (86 %) (Table 13) A mild motor disability was found in 16 patients (9 %) who displayed clumsiness impairment of balance and slight paresis. Nine patients (5 %) had a severe motor handicap The condition involved was spasticity in all cases except for one case of severe ataxia Dystonia tetra

Table 12. *Mental status after purulent meningitis according to different infectious agents*

Infectious agent	Mental level				Total
			Retardation		
	Normal	Subnormal	Mild-moderate	Severe or profound	
H. influenzae	58 (82 %)	8 (11)	2 (2 %)	3 (5 %)	71 (100 %)
Meningococcus	26 (93 %)	2 (7 %)	0	0	28 (100 %)
Pneumococcus	20 (83 %)	3 (13 %)	1 (4 %)	0	24 (100 %)
E. coli	6 (75 %)	0	0	2 (25 %)	8 (100
Other known	11 (68 %)	2 (13 %)	0	3 (19 %)	16 (100 %)
Sterile purulent	29 (81 %)	2 (6 %)	1 (3 %)	4 (11 %)	36 (00 %)
Total	150 (82 %)	17 (9 %)	4 (3 %)	12 (6 %)	183 (100 %)

Table 13. *Motor ability after purulent meningitis according to different infectious agents*

Infectious agent	Motor outcome			Total
		Handicap		
	Normal	Mild-moderate	Severe	
H. influenzae	62 (87 %)	7 (0 %)	2 (3 %)	71 (00 %)
Meningococcus	28 (00 %)	0	0	28 (100 %)
Pneumococcus	24 (96)	1 (4	0	5 (100
E. coli	5 (62 5 %)	1 (1 5)	[illegible] (5 %)	8 (100 %)
Other known	[illegible] (62 5 %)	4 (5	[illegible] (2 5 %)	16 (00 %)
Sterile purulent	27 (79 %)	[illegible] (%)	3 (9 %)	34 (100 %)
Total	156 (85 %)	[illegible] (10 %)	9 (5)	182 (100)

plegica was not found in any patient. Meningococcic meningitis was the least deleterious form of the disease in terms of motor prognosis none of the patients of this group was left with motor disability After pneumococcal meningitis only one patient had a mild motor disability whereas in the case of E. coli 37 % had a motor handicap.

Table 14 shows that only 72 % of those with neonatal meningitis had a normal mental level at the end of the follow up period. For infancy the corresponding figure was 81 % and for children 84 %. If, however the normal and subnormal patient groups are combined it appears that age at onset is no longer an important factor. Mental retardation occurred in 14 % of the neonates 9 % of the infants and 8 % of the children. As for motor functioning, 72 % of the cases with neonatal meningitis 80 % of those with meningitis in infancy and 82 % of cases of childhood meningitis were normal (Table 15) Retardation occurred correspondingly in 28 % of the neonates 17 % of the infants and 12 % of the children.

T bl 14. *Mental status and age at onset of purul t meningitis*

Mental status	Neonates	Infants	Children	Total
Normal	0 (7 %)	83 (8 %)	54 (84 %)	147 (8 %)
Subnormal	2 (4 %)	(0 %)	5 (8 %)	7 (9 %)
Retarded				
— mild to moder te	(14 %)	(%)	1 (2 %)	4 (2 %)
— severe	0	5 (5 %)	(3 %)	7 (4 %)
— profound	0	3 (3 %)	2 (3 %)	5 (2 %)
Total	4 (00 %)	01 (00 %)	64 (100 %)	180 (00 %)

Table 5. *Motor ability and age at onset f purule t meningitis*

Motor ability	Neonates	Infants	Children	Total
Normal	(7 %)	87 (83 %)	58 (88 %)	155 (84 %)
Handicap				
— mild	(14 %)	(%)	5 (8 %)	8 (0 %)
— moderate	(7 %)	(%)	0	3 (2 %)
— sever	1 (7 %)	4 (4 %)	3 (4 %)	8 (4 %)
Total	14 (00 %)	04 (00 %)	66 (00 %)	184 (00 %)

A total of 9 patients had a motor handicap prior to the onset of purulent meningitis Among these patients, the degree of disability prior to meningitis was severe in three and mild or moderate in six cases. After the disease the degree of disability remained the same in six and was further exacerbated in three patients.

Psychological prognosis In terms of psychic status 140 patients (80 %) were found to be completely normal at the follow-up examination. 25 patients (14 %) had mild neurotic symptoms and 10 patients (6 %) severe neurotic symptoms (Table 16) None of the subjects had psychotic symptoms. The proportions of both pneumococcal and H. influezae meningitis grow higher in the neurotic groups as compared with the normal group Meningococcic meningitis is relatively evenly dist

Table 16. *Psychic state after purulent meningitis related to infectious agent*

Infectious agent	Psychic state			Total
	Normal	Mild neurotic	Severe neurotic	
H. influenzae	52 (75 %)	1 (18 %)	5 (7 %)	69 (100 %)
Meningococcus	21 (78 %)	5 (19 %)	1 (3 %)	27 (100 %)
Pneumococcus	19 (70 %)	5 (19 %)	3 (11 %)	27 (100 %)
E. coli	5 (83 %)	1 (17 %)	0	6 (100 %)
Other known	16 (100 %)	0	0	16 (100 %)
Sterile purulent	27 (90 %)	2 (7 %)	1 (3 %)	30 (100 %)
Total	140 (80 %)	25 (14 %)	10 (6 %)	175 (100 %)

Table 17. *Psychic state after purulent meningitis according to age at onset*

Psychic state	Neonates	Infants	Children	Total
No symptoms	8 (73 %)	80 (81 %)	52 (80 %)	140 (80 %)
Mild neurotic symptoms	2 (18 %)	13 (13 %)	10 (15 %)	25 (14 %)
Severe neurotic symptoms	1 (9 %)	6 (6 %)	3 (5 %)	10 (6 %)
Total	11 (100 %)	99 (100 %)	65 (100 %)	175 (100 %)

Table 18. *Occurrence of expansive hydrocephalus after purulent meningitis related to infectious agent*

Infectious agent	No hydrocephalus	Hydrocephalus	Total
H. influenzae	69 (97 %)	2 (3 %)	71 (100 %)
Meningococcus	26 (100 %)	0	26 (100 %)
Pneumococcus	25 (96 %)	1 (4 %)	26 (100 %)
E. coli	6 (55 %)	5 (45 %)	11 (100 %)
Other known	12 (55 %)	10 (45 %)	22 (100 %)
Sterile purulent	30 (97 %)	1 (3 %)	31 (100 %)
Total	168 (90 %)	19 (10 %)	187 (100 %)

ributed among all the psychic status groups. A total of 73 % neonatal meningitis cases were free of psychological symptoms. Of the cases of infantile or childhood meningitis 80 % were free of symptoms (Table 17). Both mild and severe neurotic symptoms were correspondingly the more frequent the older the patient was at the onset of meningitis.

Expansive hydrocephalus. Every tenth purulent meningitis patient developed expansive hydrocephalus. Its occurrence was related to the patient's age at the onset of meningitis; 25 % of neonatal cases but only 10 % of infants and 6 % of children developed expansive hydrocephalus as an aftereffect of meningitis. Table 18 shows clearly that E. coli meningitis particularly when occurring in the neonatal period causes hydrocephalus most frequently. The "other known" bacteria can also be classified among those organisms most frequently associated with hydrocephalus. Other bacteria led to an increase in the risk of hydrocephalus only of a few percent. Delayed treatment for meningitis did not lead to a statistically significant increase in the incidence of hydrocephalus.

Epileptic fits. 10 patients (6 %) had had epileptic fits already before the onset of pu

rulent meningitis. In the acute phase of the disease 69 % of the patients had convul sions. After meningitis 14 patients (8 %) had recurring epileptic fits. Only one of the four patients who had not had seizures before meningitis still had them after the disease. All of those four patients also had convulsions in the acute phase.

Sensory defects A total of 16 patients (9 %) were found to have sensory defects after meningitis. Of these the defect had been present in three cases already prior to meningitis. In ten cases the defect came into existence during meningitis in infancy and in four cases after infancy Neonatal meningitis was involved in only two cases. The organisms most prominent in the cau sation of sensory handicaps were pneumococcus responsible for six cases (40 %) and H. influenzae which accounted for four cases (26 %) If the defects which were present already prior to meningitis and which were perhaps further exacerbated by this disease are not taken into account, it appears that pneumococcus and H. influenzae were causative of 77 % of the sensory defects. Impairment of sight had taken place in nine patients, four of them had had meningitis in infancy and five after infancy Impaired sight occurred most frequently in the bacterial category termed other known agent In four patients (11 %) The group second to it was that of pneumococcal meningitis after which two patients (1 %) were left with impaired sight. In addition one case caused by H. influenzae and one of sterile purulent meningitis had impair ment of sight. Hearing loss was found in a total of 16 patients (9 %) Seven of these (4 %) had been infected with H. influen zae and four (2 %) with pneumococcus Hearing impairment was thus most fre quent in connection with pneumococcal (10 %) and H. influenzae meningitis (9 %) A total of 9 % of the patients also had a hearing defect in the category other known None of those who had been infected with E. coli had sensory defects.

Social prognosis

Social achievement. In assessing the level of social achievement of the patient the factors taken into account were the pa tient's motor functioning, his level of intel ligence psychic status functional and working ability and other pertinent factors on the basis of which an overall picture of his possible dependency on other people was formed taking into consideration also his age. A total of 152 patients (84 %) were able to function adequately in terms of their age (Table 19) Slight or moderate de pendency on other persons referring to a need for help e.g. in dressing, moving under difficult conditions *etc* but not a need for the constant presence of another person

Tabl 9 *Personal dependency fter purulent m ngitis related to infection gent*

Infectious gent	Dependency: No dependency	Slight moder te	Great-complete	Total
H influenzae	6 (26 %)	6 (8 %)	4 (6 %)	
Meningococcus	26 (96 %)	(4 %)		71 (1[illegible]
Pneumococcus	20 (80 %)	5 (20 %)		7 (100
E. coli	5 (62 5 %)	(12 5 %)	2 (25 %)	5
Other know	(58 %)	1 (6 %)	5 (26 %)	8 [illegible]
Sterile purulent	7 (24 %)	(3 %)	1 (3 %)	3 [illegible]
Total	5 (84 %)	7 (9 %)	2 (7	[illegible]

occurred in 17 patients (9 %). Extensive or complete dependency on other persons with a need for constant supervision was found in 12 patients (7 %).

The distribution of H. influenzae meningitis corresponded to the mean distribution of the entire sample. In the case of meningococcus and pneumococcus on the other hand none of the subjects was dependent on others. The group of subjects extensively or completely dependent on others included more cases of E. coli and other known. Those patients whose CSF was sterile due to earlier antibiotic therapy were relatively seldom dependent on others.

In comparing the age at the onset of the disease it appears that complete age adequate independence and social achievement were best in the patients who had had meningitis later in life (Table 20). In accordance with this dependence on other persons occurred most frequently and was most severe in those subjects who had undergone neonatal meningitis. Extensive or complete dependence was found in 15 % of cases of infection in the neonatal period, 6 % of those who had the disease in infancy and 4 % of the oldest patient group.

Table 20. *Personal independency of patients after purulent meningitis according to age at onset*

Independence	Neonates	Infants	Children	Total
Complete independence	10 (77 %)	5 (83)	57 (88 %)	152 (84 %)
Slight to moderate dependency	1 (8 %)	(11 %)	5 (8 %)	17 (9 %)
Extensive to complete dependency	2 (15 %)	7 (6 %)	3 (4 %)	12 (7 %)
Total	13 (100 %)	103 (100 %)	65 (100 %)	181 (100 %)

The type of day time care provided for the patient varied naturally according to the need for care; of the group displaying age-adequate independence 86 % were taken care of at home, 8 % attended a full time day nursery and 6 % were somewhere else, usually in institutional care for a reason unrelated to meningitis. In cases of mild or moderate dependency care was provided at home for 88 % of these patients and in institutions for 12 %. Of the extensively or completely dependent patients 42 % were taken care of at home, 8 % in full time day nurseries and 50 % in institutions.

School attendance. At the end of the follow up period, 37 children (12 %) were not yet of school age (7 yrs.). Of those who had reached this age 7 children (3 %) were not yet mature enough to begin school. Elementary school was attended by 69 children (38 %) and secondary school by 68 children (38 %). The infectious agent was not related to the type of schools.

Type of main activity. A total of 78 patients (44 %) were either working outside the home or attending various schools and 91 subjects (51 %) were housewives or otherwise working at home. Only 5 patients (3 %) were in institutional care and 4 (2 %) were receiving disability pensions. Factors concerning the aetiology of purulent meningitis were not related to the type of main activity. On the other hand none of those who had been infected with E. coli were among the persons working or studying. In these cases however age rather than the causative organism was the contributing factor to the outcome.

DISCUSSION

The present study is concerned with 244 children treated for nontuberculous purulent meningitis in the Paediatric Department of the University of Turku during the years 1948—1972 and with the retrospective follow up of those 178 patients who survived. At the end of the follow-up period, which lasted an average of 12 years the patients were evaluated in terms of their clinical and social status and some conclusions were drawn as to the factors that might have significance for the prognosis.

There are some previous studies available concerning purulent meningitis in Finland (13 17—19 26) but these studies date back as far as the 1950's.

A clear 5 year periodicity can be distinguished in the occurrence of acute purulent meningitis, which varies between 1 and 8 per mille of the total number of hospital admissions. Our attention is particularly drawn by the fact that the very high figures of meningococcus carriers found in the Turku area in the 1960's (36) were not reflected in increased incidence figures. Finally it should be mentioned that meningococcic meningitis which has occurred in great numbers in Finland since 1973 is not within the scope of the present study

The proportion of children admitted to hospital for meningitis from among the total number of non-surgical paediatric cases has clearly decreased during the the last ten years. The average incidence was 3 9 per mille over the years 1948—1972, 3.4 per mille if meningococcic meningitis is excluded. The latter figure is somewhat smaller than the corresponding 4.4 per mille obtained in a Scottish study (8)

The parent's or guardian's occupation did not differ at a statistically significant level, as compared with the Finnish population as a whole. In the population as a whole 51 5 % belong to the three lowest strata (out of a total of nine) (28) whereas in the present study only 23 % of the parents were so classified. On the other hand, the three highest strata account for 1 7 % of the population as a whole but only 1 0 % of the parents in this study A majority of the patients thus come from the middle strata.

The type of day care provided for the child might be assumed to be a relevant factor in the occurrence of acute meningitis. The subjects of the present study date from a time when the development of privately or publicly organized daycare was not yet far advanced. However the number of children taken care of through organized day-care began to increase in Finland in the 1960's According to the results obtained in the present study a modern children's institution or an adequately supervised kindergarten or nursery school is not a factor increasing the incidence of meningitis, even though the opposite might be assumed on the basis of the studies concerning healthy carriers among men serving in the armed forces (36)

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ding to the literature (1 2 29) however its proportion is on the increase; this ten dency could not, however be verified in the present study

Comparisons between the prognostic data concerning cases with neonatal meningitis in the present study and the results reported previously in the literature are summarized in Table 21 The lethality rate has clearly decreased over the years even

Table 21. *Prognosis of neonatal purulent meningitis according to the literature*

Author(s)	Year	No. of patients	Survived acute stage		Died early
			Normal	Abnormal	
Ziai & Haggerty (40)	1958	83	7	8	75
Groover et al. (12)	1961	39	?	?	67
Dyggve (6)	962	20	30	30	40
Yu & Grauaug (39)	963	47	3	17	60
Berman & Banker (4)	1966	29	3	5	7
Fosson & Fine (9)	968		5	9	76
Overall (5)	1970	25	20	20	60
Bush (5)	97	28	50	8	32
McDonald (22)	972	82	<20	>30 %	5
Present series	1977	38	42	3	45

though still today nearly one-half of neona tes who contract meningitis die. The figu res are particularly high for premature in fants (25) In addition approximately every fifth neonate (in the present study approx. eighth) is left with some kind of neurologic defect. The probability of complete recovery thus varies between 3 % and 50 % (Table 21) In our sample it was 42 %.

H. influenzae is the most common cau sative organism in the present study as well as in those carried out previously (3 17 32) and its proportion is claimed to be on the increase (23 33) a trend which was also supported by the results of the present study

A total of 77 % of the surviving cases who had been infected with H. influenzae were healthy while the rest had either mild (17 %) or severe (6 %) sequelae. In a study by Bergstrand et al. (3) 7 out of a total of 92 subjects who had contracted purulent meningitis during the years 1947 —1957 died. A follow-up examination could be carried out on 77 patients. Of these 62 (81 %) were healthy and 15 (19 %) had a more or less severe neurologic disability In the study of 86 patients by Sell et al. (31) which covered the years 1950—1964, a total of 11 patients were found at the follow up to have died. Of the 75 survivors, 37 (49 %) were healthy 12 (16 %) mildly disabled and 26 (35 %) Sproles et al. (35) reported that 33 of his sample of 40 patients survived; among these 18 (55 %) were completely healthy whi le 11 (33 /) were moderately and 4 (12 %) severely disabled. In Hutchison and Kovac's (14) study 59 % of the patients followed up were healthy 12 % severely disabled and 29 displayed emotional symptoms.

A total of 93 % of those who underwent meningococcic meningitis had no symptoms in the present study The remaining 7 % were mildly or at most moderately disabled. Severe disabilities were not found among them at all. None was left with a motor disability Even in the pre antibiotic era those who survived meningococcic me ningitis usually recovered fully e.g. in the study by Neal et al. (24) 82 / of th survivors were healthy Farmer (7) found

in his study that 26 out of a total of 300 survivors had neurologic complications most commonly involving cranial nerves.

In this study patients with pneumococcal meningitis were also free of severe neurologic sequelae whereas mild defects were found in 22 % of the subjects. In the study by Spink and Su (34) which involved both children and adults 41 patients survived. Of these at least 9 (21 %) had serious complications. All of the disabled except for one were under 12 years of age at the onset of the disease. According to Fröber and Müller (11) disability due to meningitis could not have been reduced by administration of large doses of antibiotics as is indicated by the fact that 50 % —60 % of the survivors are still disabled exhibiting various degrees of handicap

In the present study no statistically significant differences were found in the comparison of the onset periods 1948—66 and 1967—72

The level of intelligence was normal in 82 % of the entire sample and subnormal in 9 %. Mild or moderate retardation took place in 3 % and severe retardation in 6 %. Bergstrand et al. (3) reported that 6 % of his patients were found to have suffered mental retardation. Hutchison and Kovacs (14) found normal mental functioning in 93 % and retardation in 7 % of their subjects at their follow up study

Mental development continued normally after meningitis in 72 % of the neonates 81 % of the infants and 84 % of the children Motor development was likewise normal in 72 % of the neonates 83 % of the infants and 88 % of the children. It is surprising, however that if the mildly and severely mentally disabled are taken into account the differences are remarkably small neonates 28 % infants 19 % and children 16 %. The figures for the normal continuation of motor development show a similar tendency neonates 28 % infants 17 % and children 12 % It may thus be concluded that, irrespective of the causative organism the older the child is at the onset of the disease the more complete is his recovery A factor which has a bearing on this besides age of the patient in itself is the fact that a correct diagnosis is more easily made in the case of an older child.

In a country such as Finland with the high Scandinavian standard of living, the social status of the family seems to be unrelated to the occurrence of disability in the child as it is to the lethality of the disease.

With respect to psychic status 140 patients (80 %) were completely normal, 25 (14 %) were mildly neurotic while 10 patients (6 %) had severe neurotic symptoms. Psychotic symptoms were not found in any subject. The suicide that occurred during the period of the study may have involved a meningitis-related psychological disturbance but no demonstrable association with this disease was found for it. When psychological symptoms are compared with age at the onset of illness the tendency for the prognosis to improve with increased age no longer occurs for apart from the neonatal group (27 %) both the infants and the children have approximately the same extent of psychological symptoms (19 % and 20 %) To what degree these are psychological symptoms caused by illness and hospitalization *per se rather than* symptoms caused by meningitis is difficult to say

In the present study expansive hydrocephalus developed in every tenth patient. Its occurrence seems to be associated with age at the onset of meningitis and not with the infectious agent, as indicated by the fact that neonatal meningitis led to hydrocephalus in 25 % of cases compared to only 6 % of those who contracted the disease after infancy Neonatal meningitis combined with E. coli seemed to have the worst outcome of all whereas meningitis caused by other bacteria increased the risk

of hydrocephalus by only a few per cent. Delayed treatment for meningitis seemed not to increase the occurrence of hydrocephalus significantly. The frequency found here for hydrocephalus is remarkably high compared with the data reported in literature (3, 16, 20); on the other hand, found that in 34 % of those who had undergone purulent meningitis the enlargement of the head was at least 3 cm over the normal values for the age groups concerned, which may in most cases indicate at least potential hydrocephalus.

Recurring epileptic fits occurred after meningitis in 14 patients (8 %). Of these, however, 10 cases had already had sporadic or recurring fits prior to the onset of meningitis so that the effect of meningitis in increasing the occurrence of epilepsy was relatively small.

Among the sensory handicaps defects in hearing and sight were most common. In this group more than three in four had been infected either with H. influenzae or pneumococcus. The role possibly played by medication in impairment of hearing could not be discovered reliably. The effect of meningitis on the senses of smell and taste also remained unknown.

The social competence of the patient is influenced by a large number of factors among which changes due to the disease itself, such as motor functioning, the level of intelligence, emotional condition, sensory functioning and other higher cerebral functions form only a part. Environmental factors may play a fairly considerable part in the rehabilitation of the patient. In our study 84 % of the survived patients were able to attend their everyday needs at a level quite adequate to their age. The best outcome was observed in those who had undergone meningococcal meningitis in whom neurologic defects were not found as frequently as in the other forms of the disease. Antibiotic therapy given prior to the diagnosis of meningitis also seems to have a beneficial effect. Neonatal meningitis led in every fourth case to extensive or complete dependency on other persons and frequently to institutional care.

The main activity of the patients consisted of gainful employment in a third of the subjects. One-half of the patients either had not yet reached school age or were children of school age under 16 years old who were not mature enough to go to school. In addition, some had completed their school but were not gainfully employed outside the home. Every eighth subject was in school or at college. Pensioners living in their own homes accounted for 2 % and those in institutional care for 3 % of the subjects. Although the classification employed fails to give a complete picture of the everyday activities of the subjects, it serves to demonstrate that only very few were not engaged in any kind of productive activity. Thus meningitis need not lead to the loss of functional and working ability except for at most 10 % of those who contract the disease.

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Procedural Manual

By E. HOFMANN, B. HAVENS, S. GEIDEL,
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*From Newborn Division of the Los Angeles County University of Southern California Medical Center
Department of Pediatrics University of Southern California,
School of Medicine Los Angeles, California*

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1 INTRODUCTION

The objective of this manual is to describe monitoring techniques and procedures for ac quisition of high quality signals over at least twelve-hour periods. The techniques de scribed were developed for use with full-term newborns and infants up to the age of six months Such a long-term monitoring paradigm offers certain technical challenges Infant needs for nursing care as well as their uncoordinated mass activity tend to make ac quisition of physiological signals difficult. The key to high quality recordings is careful prep-aration, thus cannot be overemphasized Ap-propriate preparation of the infant and care-ful application of the electrodes and transduc ers prevent not only loss of signals and data, but also eliminate interruption of sleep pat terns. While it is true that electrodes can be reapplied at convenient times such as after feedings, experience has shown that such reapplication jeopardizes other signals that previously were good and often unnecessarily upsets the infant

The first aspect of preparation involves readying of the facility and equipment in advance of the infant s arrival The second most important aspect is the adherence to a sequence and timing of events While a routine procedure covering the entire preparatory and monitoring stages is important, this procedure cannot be followed rigidly Modifications and adjustments need to be made which are de pendent on each individual infant and his state at the time of arrival. It is therefore im-portant that about thirty minutes be allowed for the evaluation of certain parameters before any application of electrodes or transducers.

An unhurried talk with the infant s parent or caretaker prior to monitoring is reassuring and reduces tension in both parent and infant Monitoring procedures are discussed with reference to illustrations from a photograph album, and appropriate consent forms signed. A tour of the facility is given, and mothers are permitted to stay overnight if they choose. This can be especially useful if the baby is breast fed The mother s presence is often de sirable both for the benefit of the infant and for the parent's continued satisfaction with monitoring participation A relaxed mother may calm the infant during set-up and waking periods. Facilities should therefore be made readily available to the parent who chooses to stay with the infant.

Information about the infant s current health status, feeding menu and schedules and idiosyncratic sleep habits (most comfortable position, use of pacifier etc) is obtained Rec tal temperature general physical assessment and inspection of the skin should be performed before the parent or caretaker leaves

Infants may be hungry on arrival. Solid foods can be given before preparation begins in older babies and bottle or breast feeding is provided for all age groups during the applica-tion of head electrodes.

Frequently parents bring the baby in later than scheduled it may be tempting to increase the pace. It is however very important not to rush the preparation. Ultimately it is more advantageous to have fewer hours of a high quality recording than many hours of poor quality data.

Chapter Two provides a detailed description of preparing the infant for monitoring.

Chapter Three outlines the standard moni-toring procedure and discusses the need for charting of events to aid subsequent data in-terpretation.

An important component of preparation is

signal evaluation adjustment and maintenance It is important to minimize equipment adjustments after the onset of taping especially if data are taped for future computer analysis Therefore it pays to allow ample time to evaluate the signal quality and make the necessary adjustments Guidelines for this stage of preparation are provided in Chapter Four

2. APPLICATION OF ELECTRODES AND TRANSDUCERS

GENERAL

This chapter deals with the preparation of the infant for monitoring. The techniques described are non invasive A discussion of the scientific implications of data thus obtained is beyond the scope of this manual

Transduers and other supply items mentioned in the text have been shown to yield good results Some have been chosen because they can be readily gas sterilized and others because they are disposable Inclusion of items does not mean that other adequate substitutes are unavailable on the market

The sleep parameters included in the array are two EEG derivations one eye movement signal somatic activity and chin muscle tone (EMG)

The cardiopulmonary variables discussed - one EKG derivation and three different estimates of respiration An impedance technique is utilized to measure chest excursions A cessation of breathing evidenced in this channel would indicate a central apnea. A thermistor bead in the vicinity of the nares estimates air flow through the nose Both techniques are artifact prone Addition of a pCO_2 sensor yields artifact free respiratory signals We employ a Beckman CO_2 analyzer which does not however provide accurate estimate of end-expiratory pCO_2 in infants without instrument modification

The routine sequence of electrode application is as follow

A Chest Abdomen (EKG impedance and ground electrodes skin temperature probe)

B Head (EEG and EMG electrodes)

C Face (cannula eye movement sensor)

This sequence will be followed in the discussion

A CHEST AND ABDOMEN

Supplies

- Seven pregelled chest electrodes (1)
- Seven extension connectors (2)
- One skin temperature probe (3)
- Hypo-allergenic tape (4)
- Alcohol wipes
- Benzoin
- Electrode jelly (5)

Label electrodes as follows ? EKG impedance resp (chest) 2 impedance resp (belly) and 1 ground

Application

While the infant is undressed observe the breathing pattern The optimal location of *impedance electrodes* is over the areas of greatest excursion Photograph 1 shows the electrode placement to record thoracic respiration motion It is important that the sites are equidistant from the midline and at the same level maximal separation of electrodes and symmetrical placement are *essential* for a good recording. Photograph shows the desirable application sites when abdominal respirations are recorded We utilize both methods when monitoring and employ a manual switch box to change modes of recording as necessary throughout the night



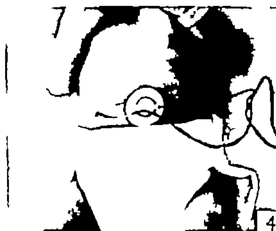
Photograph 1 Location of impedance electrodes to re cord thoracic respiratory motion. Not the symmetric placement on the axillary line.



Photograph 3 Location of ECG electrodes. An area beneath the cla icles was chosen so that head motion does not introduce artifact; equidistance from the midline is necessary



Photograph 2 Location of impedance electrodes to re cord abdominal respiratory motion. Note again the symmetrical placement



Photograph 4 Application site of the ground electrode on the midline above the umbilicus. The temperature sensor has been applied to the skin over the liver with hypoallergenic tape.



Photograph 5 Newborn infant swaddled to limit arm movements.



Photograph 7 Hand position while abrading the skin sites with a cotton swab dipped in acetone-alcohol.

The optimal application sites for EKG electrodes are indicated in Photograph 3 An area far enough beneath the clavicles should be selected in small infants so that head motion does not interfere Equidistance from the midline is essential

The application sites for the *ground* electrode is exactly at the midline immediately above the umbilicus. Thorough cleansing of this area will assure good contact (Photograph 4)

To apply electrodes examine the chosen sites for irritation If the baby is perspiring heavily or has a fragile skin Benzoin should be applied to the adhesive portion of the electrodes. Also if the active part or the eye of the electrode is dry supplement with jelly Otherwise clean the areas thoroughly with an alcohol wipe and rub vigorously a small amount of electrode jelly (5) into each site until the skin is again dry to the touch Apply labelled electrodes as indicated Check and record skin resistances of each set of electrodes with an ohm meter Make sure electrodes and jellies are used before the expiration date

The *skin temperature sensor* (3) should be taped over the liver with the shiny side of the disk against the skin (Photograph 4) After



Photograph 6 Determination of EEG electrode site with modified compass and tape measure



Photograph 8 An EEG covered with a small cotton ball.

application of these electrodes the infant is dressed for the night, a one-piece terrycloth stretch suit is ideal. This apparel provides warmth during the night and eliminates the need to intervene if the infant kicks off the blanket it is also manageable for diapering. The leads are joined and brought over the shoulder At this time elbow restraints are applied to young infants newborns may be swaddled in a blanket (Photograph 5)

B HEAD

Supplies

- Six silver-chloride cup electrodes soaked in normal saline for a minimum of one half hour (6)
- Transpore tape 1 inch (7)
- One roll of four and one-half inch six ply gauze or Kerlix (8)
- Electrode paste (9)
- Modified compass and/or tape measure
- Acetone-alcohol
- Cotton Swabs
- Cotton Balls

EEG

This application is best performed while the infant is quiet, a bottle or breast feeding at this time provides both a method of calming an active infant and a preparation for later sleep The infant should be held in a comfortable position by an assistant.

Assess the condition of hair and scalp Hair treated with pomades and oils, or a scalp with cradle cap should be thoroughly shampooed and rinsed prior to electrode application. Hair must be allowed to dry

To mark the sites for EEG electrode application begin by locating the midpoint on the skull using ears and nose as reference points Measuring 1 5 centimeters to either side of the midline mark the scalp for site number one. Similarly measure 6 0 centimeters to either side of the midline as site number two (Photograph 6)

Now e aluate these sites *If you find them* on a fontanel or sutures which are separated or overriding then slightly alter the sites bilaterally to a firm intact cranial surface Note also that the distances from the midline may vary slightly with infant age or head size such changes however should be bilaterally equal for that infant. Using cotton swabs, separate the hair on one side and thoroughly clean the scalp with acetone-alcohol Use a firm back and forth stroke and enough pressure to abrade the skin (Photograph 7) Severe cradle cap or hyperkertotic newborn skin is a problem and several dry layers may need to be removed. For a good application, some abrasion is necessary but care must be taken not to scrub too vigorously and cause injury

Maintain the hair separation and site location with one hand, and with the other rub a small amount of paste (9) into the prepared site. Dry the electrode cup (6) and fill with paste until slightly overflowing. Push it firmly onto the prepared skin covering electrode and paste with a small cotton ball (Photograph 8) Push firmly on the electrode for about one minute to ensure good contact. Prepare the other sites in a similar manner Throughout this period it is essential to periodically apply firm pressure to each electrode so that good contact is maintained during drying. Note for future reference the location of your electrodes, either by color coding or direct labeling of each lead.

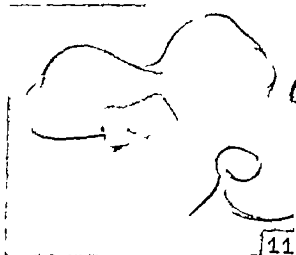
EMG

Begin by selecting your two sites for electrode application. Site number one is at the tip of the chin (Photograph 9) site number two is located on the belly of the digastric muscle just to the left of the infant's trachea. It is easiest to find this spot by encouraging the infant to suck and simultaneously palpating the area of greatest muscle reaction (Photograph 10)

Cleanse both sites with acetone alcohol swabs, again abrading the skin lightly Allow the skin to thoroughly dry While the skin is drying the electrodes can be prepared. Tear off a two-inch strip of one-inch tape (7) and



Photograph 9 While the EEG electrode paste is dry ng, the sites for the EMG lectrodes can be prepared Th photograph shows the abrasion of site number 1 the tip of the chin or mental prot berance.



Photograph 11 Demonstration of electrode threaded through a t -inch strip of one-inch hypoallergenic tape

thread the electrode cup through for increased stability (Photograph 11)

Fill the electrode cup with paste to the rim only (too much paste will spill over and weaken the application) and apply to site number one Pleat the tape as you press it to the skin to achieve good conformity with the chin contours Reinforce these pleats with one-half inch wide tape strips

The electrode at site number two is applied most easily with the infant s neck slightly extended. Observe him/her carefully during this period for cyanosis or respiratory difficulty Apply the electrode at site number two in a similar manner and reinforce it with a second strip of one-inch tape (Photograph 1?)

Head Wrapping

In order to ensure even pressure on the EEG electrodes and to protect them throughout the



Photograph 10 Palpation of the diga tric muscle t locate EMG site number 2



Photograph 12 An infant instrumented w th EMG electrodes.



Photograph 13 Initial lateral wrap over the electrodes and under the chin.





Photograph 14 and 15 Continuation of head wrapping to the anterior–posterior plane. After completion of the head wrapping, both EEG and EMG electrode leads are secured to the Kerlix on the left side of the head with tape strips.

night, the head is wrapped in a roll of four and one-half inch six ply gauze (8) Begin by pressing firmly on each scalp electrode It is important that at least fifteen minutes drying time has elapsed since their initial application and that the paste has begun to harden. If wrapping is done too soon, electrodes may slide and bilateral symmetry will be lost. Be certain that electrodes remain separate that is the paste in one electrode must not be in contact with that in any other forming a bridge Small bridges can be eliminated by cleaning the space between electrodes with cotton swabs saturated with acetone-alcohol If this is not effective a total reapplication of that side is necessary Check and record resistances of electrode pairs with an ohm meter or other appropriate measuring device

For easiest wrapping, place the infant in a supported sitting position Begin with a firm lateral wrap extending over the electrodes and under the chin. Repeat this for two–three circles (Photograph 13) Next, wrap the gauze in an anterior–posterior plane being sure to bring down under the back of the head each time for a secure hold (Photograph 14) This wrap usually takes about one-half roll of standard width Kerlix For exceptionally small infants it may be necessary to split the Kerlix longitudinally

Be sure to wrap with a firm and even pressure This can be a most important step in achieving a high quality long-lasting signal. Secure the Kerlix ends with tape Similarly attach EEG and EMG leads to the left side of the head with short tape strips (Photograph 15) Return the infant to the crib

C FACE

Nasal Cannula

Supplies

– pCO cannula with thermistor (see Chapter 5)



Photograph 16 Placement of the nasal cannula in the nostrils.

– Two strips of one half inch tape each approximately one inch in length

When the infant is on his back in the crib and an assistant is stabilizing his head insert cannula tips into the nostrils and tape the tubing to each cheek Pinch the tape firmly around the tubing and check its adherence to the skin (Photograph 16 and 17) A loose fit will quickly fall off with activity It is important that the cannula is not bent or stretched during this application The ther mistor bead is small fragile and easily broken.

Eyepiece

Supplies

– One eyepiece (Harper et al 1975)

– One half inch tape four strips each about four inches long

With the infant on his back apply the eyepiece over the left eye with its inner edge resting on the lateral surface of the nose Se cure on four sides with tape strips It is usually easiest at this point for an assistant to hold the eyepiece and the infant s head while another person tapes it down (Photograph 18)

The infant can now be positioned and quieted for sleep The supine position is pre



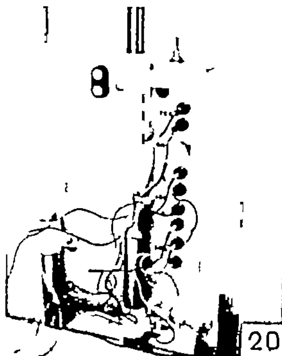
Photograph 17 Completed application of the nasal cannula



Photograph 18 Completed application of eye movement sensor



Photograph 19 Infant prepared for long-term monitoring.



Photograph 20 Miniature amplifier unit mounted on the crib bars.

ferable since interference with chest and facial electrodes is minimal. Placing a young infant in the supine position necessitates constant surveillance in case the infant spits up The side-lying position (infant s back propped with a blanket) is adequate even though the chest impedance and EKG signal may be affected more readily by movement. The prone position although often preferred by the infant is least satisfactory since the facial electrodes are readily disturbed. Thus the infant is never placed in the prone position If however the infant turns onto his stomach during sleep as an older infant is inclined to do no intervention is made as long as the signals remain adequate. While one of the staff members positions and quiets the infant the assistant can make all connections to the pin board and straighten the room for the night s recordings (Photograph 19)

3 MONITORING PROCEDURE

Newborn infants sleep throughout the twenty four hour day with interruptions for feeding and care. The typical day time wakefulness and night time sleeping pattern is not established until about three or four months of age (Parmelee 1961 Parmelee et al 1964) Continuous monitoring is made easier when the infant sleeps Evening and night time monitoring is therefore desirable for older infants whereas the time of day may be less important for newborns. Uninterrupted monitoring is rarely obtained. Infants are irritated to a varying degree by the monitoring process and show a larger number of sleep interruptions than if they were asleep at home Meticulous preparation reduces the number of induced awakenings for the purpose of electrode reapplication. The number of spontaneous awakenings depends on the infant his health status age and home sleeping patterns

Interventions of three kinds can be

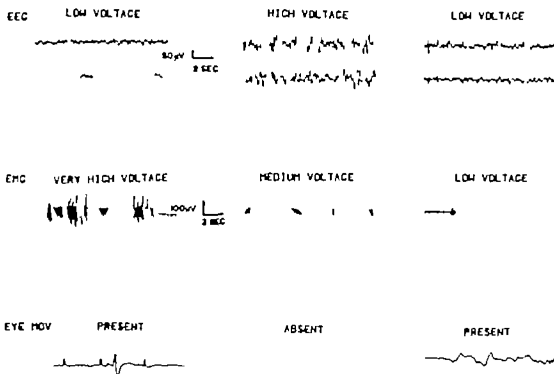


Figure A. This figure illustrates typical polygraph tracings obtained from the same infants during different behavioral states. Note differing patterns of low and high voltage of the EEG and EMG and presence or absence of eye movements.

identified Infant care needs interventions to readjust or reapply an electrode and changes in equipment settings

Infant needs involve feeding diapering and comforting. In our unit Infants are fed on a demand schedule A bottle fed Infant (newborn–two months) generally awakens every two to four hours for a feeding of one to four ounces A newborn breast fed infant may awaken more frequently and have smaller feedings As an infant grows the amount per feeding and duration between feedings increases For most formula fed newborns it is advisable to burp the infant every half to one ounce of milk. Older infants should be burped after consuming two ounces While the infant cannot be removed from the crib at anytime during the monitoring, his upper body can be held upright and supported during the feeding and burping. The length of the electrodes should allow for a seated position. The child is diapered in a supine position before or after the feeding. We have found disposable diapers to be convenient

A crib of at least waist height is optimal for the breast feeding mother She leans over the crib and holds the infant to her breast and is able to cuddle the child Initially the procedure is often uncomfortable for the mother and help with positioning as well as encouragement may be needed

Fussiness may continue in spite of meeting the infant s feeding and diapering needs If an infant is accustomed to being held at home he may need extra tactile contact. The older infant accustomed to being awake and active at

a particular time may require company and verbal stimulation. Sometimes the infant merely needs to have a "fussy period" Signal quality will return after the "fussy period"

It is advisable to write a protocol for the monitoring staff which specifies permissable equipment adjustments Data reduction strategies dictate which signals should or should not be adjusted during the monitoring The decision to interrupt sleep in order to reapply or readjust an electrode should be made on the basis of signal importance. Such a protocol will vary with the purpose of each study

In order to interpret the data later a system of charting must be followed Behavioral observations are made on the chart with both pencil and coded keys The behaviors to be charted include eyes open or closed feeding or sucking awake or asleep gross movements vocalizations. In addition incidences of infant manipulations and equipment adjustments need to be noted on the polygraph paper A video monitor helps to observe the infant. A signal log (Appendix I) is kept to record the quality of channel output hourly and to facilitate communication between monitoring shifts and engineering staff A feeding and infant care log may be helpful as well (Appendix II)

An oscilloscope is essential to monitor the quality of the signals being taped especially if the order of data acquisition consists of infant-polygraph amplifiers and subsequently in parallel polygraph pens and tape recorder An alternative way to monitor the quality of the taped signals is to modify this order to infant polygraph amplifiers and then in series tape recorder polygraph pens

Continuous monitoring is feasible but requires vigilance. The presence of two staff members is considered necessary and monitoring staff rotation every one to two hours has been useful in maintaining good quality recordings and charting.

4 SIGNAL EVALUATION AND ADJUSTMENT

GENERAL

The main purpose of this chapter is to provide clues for the identification of poor signals and to discuss remedies for their improvement. When a monitoring unit is located within a hospital interference from surrounding electro-magnetic fields is frequently encountered This problem can be controlled with completely shielded monitoring units the tracings discussed in this chapter however were obtained in an unshielded environment

Sufficient time should be allowed for initial signal evaluation and adjustment. An infant in a quiet though not necessarily sleeping state is essential It should be noted that several of the signals change as a function of behavioral state and these changes are in fact included in the array to allow for discrimination between sleep and waking states Notable among these are EEG eye movement and EMG Figure A summarizes the salient characteristics of these signals as a function of behavioral state.

In general when a signal is absent or shows considerable or unusual artifact several checks can be made before a decision is reached to reapply the electrodes or to substantially depart from usual polygraph settings (Appendix III)

(*a*) The position of the infant can affect such signals as the impedance respiration and the configuration of the EKG and the EEG

(*b*) *Overhead fluorescent lights* may introduce 60 cycle artifact. In addition a dimmed room is optimal for eye movement recordings

(*c*) The numbers of the selector board should be punched in properly and each amplifier turned *on* Some pieces of equipment

SOMATIC ACTIVITY

FIGURE 1A

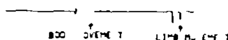


FIGURE 1B

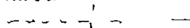


FIGURE 1C

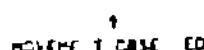


FIGURE 1D

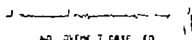


Figure 1 (A) Example of a good signal, both movements of the entire body as well as isolated limb or head movements can be identified. (B) Respiratory movements are registered on the Somatic Activity channel. Try *decreasing* the sensitivity (see arrows on examples) If the amplifier is set at the lowest sensitivity (mV scale) try placing a blanket under the infant. (C) Somatic Activity was observed at the arrow but is not registered. Increase the sensitivity If this does not improve the signal, check pin board connection and selector board numbers for accuracy (D) Unaccounted for activity is observed in the Somatic Activity channel. This may represent a transducer or equipment malfunctioning.

have settings for calibration and operations be sure that the dials are turned to *operation*

(*d*) Check to see if pinboard connections are accurate and snug and the ground lead connected. These are common causes of 60 cycle artifact on sensitive channels.

(*e*) *The impedance respiration leads must* be correctly applied and connected or the output of this channel may interfere with other signals It can for instance produce 60 cycles in one or both EEG channels

Occasionally the humidity in the facility is very low (<20%) and the quality of a recording may decrease In an uncontrolled environment this must be tolerated Also the behavior of newborns is marked by a great deal of active sleep and concomitant phasic activity such as twitches jerks and head movements *These tend to transiently introduce artifacts* especially in the EEG Two means of reducing movement artifacts may be employed. Miniature amplifiers can be affixed to the EEG electrodes applied to the infant s head Such units are not as yet commercially available. Miniature amplifiers can also be mounted as an assembly to the bed we have used this solution in our unit (see Photograph 20) Neither system however eliminates movement artifacts generated by the friction between the electrode and the scalp

The remainder of this chapter is devoted to a brief description of individual parameters examples of good and poor signals and suggestions for improvement. These recommendations apply to both initial signal evaluation and to the monitoring period

A 16 channel Grass model 78 polygraph was used throughout, but the discussion has been general to permit application to other equipment. Appendix III provides information about settings. Special purpose monitoring equipment was either purchased or assembled The details are beyond the scope of this manual Calibration procedures have been purposely omitted since these vary widely with equipment as well as with study objectives

INDIVIDUAL PARAMETERS

A *Somatic activity*

Capacitance electrodes on the mattress surface register the infant s gross body movements (see Chapter 5 for assembly)

Prior to the monitoring session run your finger nail gently over the silver strip electrodes to assure responsivity When the infant is older its weight may cause registration of respiratory movements This can be prevented by placing a blanket between the infant and the mattress During the initial signal evaluation stage assure yourself that movements of the entire body as well as iso-

IMPEDANCE RESPIRATION

FIGURE 2A

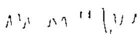


FIGURE 2B



FIGURE 2C



FIGURE 2D



FIGURE 2E

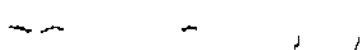


FIGURE 2F



FIGURE 2G

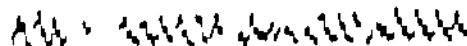


Figure 2 (A) Example of good signal obtained during Active Sleep. Irregularity in rate and depth is typical of this state. (B) Good signal during Quiet Sleep. (C) 60 cycle in the impedance respiration signal. See General Introduction for suggestions. (D) EKG in the impedance signal. Check whether lead fell off or skin contact is poor. (E) Poor signal: increase sensitivity with or without changing scales (μV→mV). At the arrow the right adjustment was made. (F) Sensitivity is too high, signal is blocked, decrease sensitivity with or without changing scales (μV→mV). (G) Heart bumps are superimposed upon the respiratory signal. This is often due to poor electrode skin contact. However sometimes spontaneous position change can remedy this as well. At the time of next awakening, reapply the electrodes. A switch from chest to abdominal recording leads may also improve the signal.

THERMISTOR RESPIRATION

FIGURE 3A



FIGURE 3B

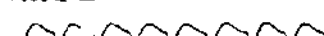


FIGURE 3C

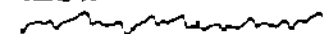


FIGURE 3D



FIGURE 3E



Figure 3 (A) Good signal obtained during Active Sleep. (B) Good signal obtained during Quiet Sleep. (C) 60 cycle in thermistor respiration signal. Probably due to broken lead. Replace entire cannula at the next feeding. The EKG is superimposed on this signal as well. This may be caused by interference from the impedance plethysmograph. Read Impedance Respiration for suggestions. (D) A poor signal. An increase in sensitivity may improve the signal. Also, the baby may be leaning on the cannula arm. Sometimes carefully moving the head or changing the infant' head position helps. If simultaneously the pCO_2 signal is of low amplitude, the nasal cannula probably slipped out of the nostrils. (E) Signal is too high. Decrease sensitivity with or without scale change (μV→mV).

PCO2 RESPIRATION

FIGURE 4A



FIGURE 4B



FIGURE 4C



FIGURE 4D

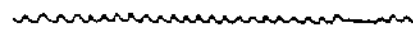


Figure 4 (A) Good signal obtained during Active Sleep. (B) Good signal obtained during Quiet Sleep. (C) Baseline shift, caused by fluid accumulation in the tubing. Replace the filter. (D) Decreased signal amplitude. This is sometimes result of fast respiration or panting. Partial plugging of the tubing may be also causing a low amplitude of this signal. If the infant is breathing normally check whether or not the cannula tips are into the nostrils. A filter change may remedy this problem as well.

SOMATIC ACTIVITY

FIGURE 1

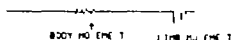


FIGURE 1B

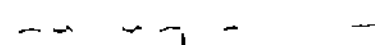


FIGURE 1C

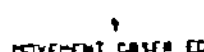


FIGURE 1D



Figure 1 (A) Example of a good signal: both movements of the entire body as well as isolated limb or head movements can be identified. (B) Respiratory movements are registered on the Somatic Activity channel. Try *decreasing* the sensitivity (see arrows on examples). If the amplifier is set at the lowest sensitivity (mV scale) try placing a blanket under the infant. (C) Somatic Activity was observed at the arrow but is not registered. Increase the sensitivity. If this does not improve the signal, check pin board connection and selector board numbers for accuracy. (D) Unaccounted for activity is observed in the Somatic Activity channel. This may represent a transducer or equipment malfunctioning.

have settings for calibration and operations, be sure that the dials are turned to *operation*.

(*d*) Check to see if pinboard connections are accurate and snug and the ground lead connected. These are common causes of 60 cycle artifact on sensitive channels.

(*e*) The impedance respiration leads must be correctly applied and connected or the output of this channel may interfere with other signals. It can, for instance, produce 60 cycles in one or both EEG channels.

Occasionally, the humidity in the facility is very low (<20%) and the quality of a recording may decrease. In an uncontrolled environment, this must be tolerated. Also, the behavior of newborns is marked by a great deal of active sleep and concomitant phasic activity such as twitches, jerks and head movements. These tend to transiently introduce artifacts especially in the EEG. Two means of reducing movement artifacts may be employed. Miniature amplifiers can be affixed to the EEG electrodes applied to the infant's head. Such units are not as yet commercially available. Miniature amplifiers can also be mounted as an assembly to the bed; we have used this solution in our unit (see Photograph 20). Neither system, however, eliminates movement artifacts generated by the friction between the electrode and the scalp.

The remainder of this chapter is devoted to a brief description of individual parameters, examples of good and poor signals, and suggestions for improvement. These recommendations apply to both initial signal evaluation and to the monitoring period.

A 16 channel Grass model 78 polygraph was used throughout, but the discussion has been general to permit application to other equipment. Appendix III provides information about settings. Special purpose monitoring equipment was either purchased or assembled. The details are beyond the scope of this manual. Calibration procedures have been purposely omitted since these vary widely with equipment as well as with study objectives.

INDIVIDUAL PARAMETERS

A. *Somatic activity*

Capacitance electrodes on the mattress surface register the infant's gross body movements (see Chapter 5 for assembly).

Prior to the monitoring session, run your finger nail gently over the silver strip electrodes to assure responsivity. When the infant is older, its weight may cause registration of respiratory movements. This can be prevented by placing a blanket between the infant and the mattress. During the initial signal evaluation stage, assure yourself that movements of the entire body as well as iso-

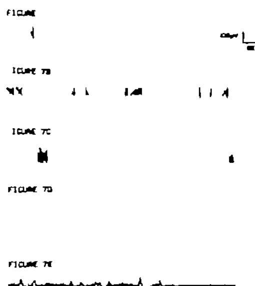


Figure 7A A good EMG during REM ith low sustained tone and the presence of short bursts. It is usual to have some EKG present at this time

Figur 7B A good EMG in Quiet Sleep with tone high and sustained. This has obliterated the previous EKG signal.

Figure 7C A strong contamination by EKG may be improved by reapplication of the electrode at site number 2 (see Photograph 2) to position more directly over the belly of the digastric muscle

Figure 7D The presence of 60 Hz is most easily detected at 15 mm/sec paper speed Follow the general rules for correcting 60 Hz interference (see Chapter Introduction) and if the signal is not improved then total reapplication is necessary

F gure 7E Periodic DC shifts may occur and can usually be eliminated by increasing the fall time constant from three to ten.

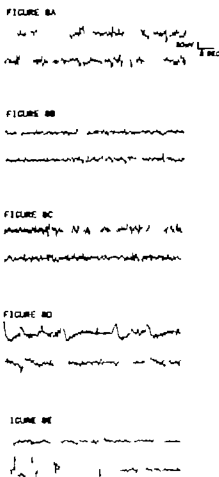


Figure 8A A good signal obtained during Quiet Sleep in one-month old infant

Figure 8B In the same infant, good REM recording is of lower voltage and faster pattern.

Figure 8C Illustrates EKG and 60 Hz contamination in the first tracing. Persistent EKG occurs when leads are over an open suture or fontanel. A reapplication must be done to eliminate this artifact. T eliminate 60 Hz, first observ general solutions (see Chapter Introduction). If not improved, then recheck skin impedance. A high reading in quiet infant can indicate poor skin contact. E en pressure applied to the electrodes through the Kerlix can sometime improv the signal. If other measures fail a reapplication is necessary

Figure 8D This figure show slow rolling baseline. Proper grounding and the Fall Time constant at the correct setting can improv the signal. There are some recordings when this situation must be tolerated.

F gure 8E Th figure illustrates loose electrode on the second tracing Manual pressure may improv the signal reapplication may be necessary

sensitivity adjustments with or without scale changes (µV to mV or vice versa) are necessary during the monitoring period.

D *pCO_2 concentration and respiration*

A sample of expired air is continuously obtained through the nasal cannula and analyzed for CO_2 concentration (see Figure 4A)

E. *EKG*

One EKG is usually obtained in sleep recordings The choice of R wave polarity is arbitrary but *computer analysis is facilitated if*

one polarity can be adhered to across recordings (see Figure 5 A)

F Eye movement

Eye movement is recorded by measuring reflected infrared light from an open or closed eye which is illuminated by an external infrared source (Harper et al 1975) An optimal setting on the eyepiece provides a baseline of slight ripples or low amplitude deflections during quiet sleep with no false positive deflections. The eyepiece output should be validated during active sleep (Figure 6 A) Changes in ambient light, the use of infrared lighting for closed circuit television monitoring or position changes of the infant s head may necessitate further adjustments while monitoring.

G EMG

The EMG represents fluctuations in body muscle tone as reflected by changes in the digastric muscle In the initial evaluation of the signal, sleep state must be considered (see Figure A) A high enough setting must be used to differentiate changes in tone with state changes

H EEG

This signal records electrical activity of the brain and characteristically varies with sleep state and age (Figure A) A good signal reflects state changes (see Figure 8 A and B) and is preserved without artifacts during at least portions of wakefulness

5 PREPARATION OF ELECTRODES AND TRANSDUCERS

A NASAL CANNULA/NASAL THERMISTOR

Supplies.

- French feeding tube (10)
- Thermistor bead (11)
- Teflon-insulated wire (12)

A number eight French feeding tube is used (10) The closure plug at the distal end of the tube is removed also removed is the proximal end of the tube containing the two holes. Another three centimeters of tubing is cut off from the proximal end and divided into two pieces which have slanted edges These are the nasal prongs for the cannula (Photograph 21) At two and three centimeters from the proximal end of the tube notches are made with a scalpel Using a scissor point the notches are widened The nasal prongs are inserted and taped into place with paper tape (Photograph) A splice is made in the proximal end of the tubing for insertion of a thermistor bead (11) The leads are connected to teflon-insulated wire

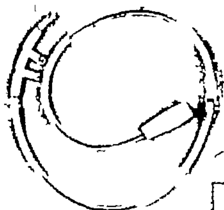
B SOMATIC ACTIVITY ELECTRODES

Supplies.

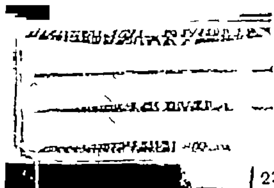
- Somatic activity electrodes (13)
- Coaxial cable (14)
- Differential amplifier (15)



Photograph 21 For the assembly of miniature cannula, we use number eight French feeding tube. Arrow indicates two nasal prongs which have been cut with slanted edges (see text).



Photograph 22 Nasal prongs inserted and taped into place with paper tape. In this picture, the thermistor bead has not been inserted yet.



Photograph 23 Movement sensor taped onto crib mattress (see text).

Somatic activity electrodes are made from the same conductive-coated mylar foil used by commercial manufacturers of capacitors (*13*) The foil is basically mylar with a thin conductive coating on one side only

Each pair of capacitor plates is formed by taping two 21-inch strips back to back with the mylar surfaces facing inward and the conductive coatings facing outward Three of these pairs are connected in parallel and all are encased in a plastic bag, ensuring that a total crib space of approximately 21 inches by 11 inches is monitored for gross body movements photograph 23)

The three bottom plates feed via coaxial (14) cable to one input of a differential amplifier (15) The top plates feed via the same type of cables to the other differential input of the same amplifier The flat plastic bag lies between the crib mattress and the crib sheet

ACKNOWLEDGEMENT

The National Institute of Health the Child *Health and Human Development Branch* invited us to do an in depth study of the development of sleep and cardiopulmonary regulation moreover they gave us funds to conduct this project. The objective of this study was to provide a description of developmental patterns between birth and six months of age in infants and to identify patterns related to increased risk for Sudden Infant Death Syndrome (SIDS) The project (Contract no NO1 HD-? ?777) was a collaborative effort involving the Newborn Division of the Department of Pediatrics Los Angeles County University of Southern California Medical Center the Department of Anatomy and the Brain Research Institute of the University of California at Los Angeles (Contract no HD4-2810) and the Veterans Administration Hospital in Sepulveda.

We have almost completed the data collection phase of this project. Approximately 400 twelve-hour recordings have been made on a total of seventy four infants. The majority were monitored at monthly intervals until they reached the age of six months. *This manual* describes in detail the procedures we utilized.

Many people contributed to this data collection effort. By returning their infants every month the parents indicated they appr

and trusted both the clinical and monitoring staff Drs Chester Martin David Sachs Bruce Ettinger Patricia Little and Richard Lowensohn were obstetricians for the project. Many nurses worked part time. Each contributed their skills time and especially their caring for the infants parents and their colleagues Their names deserve to be mentioned

Ester Doremus	Sarah Lara
Cecilia Gallerito	Terri Marrinan
Pat Gibbons	Michele Morin
Wendy Richie Haldeman	Susan Reutimann
	Eva Sakamoto
Sharon Harris	Marsha Sato
Margo Herman	Lorraine Sterman
Rosalie Hummel	Janet Uzane
Lorie Judson	Caro van Valkenberg

Other professionals helped them with the monitoring and developmental evaluations.

Diane Combs	Ruth Tiongson M D
Laura Litow	Lorraine Whittman

Drs Mary Ellen Freedman Anthony Hadeed and Martha Gutenberg supervised the clinical course of the infants during the sessions.

An equipment oriented project relies heavily on its engineering department. Dr Edward Hon s engineering staff contributed invaluable technical skills They are Mr Jiri Jilek, chief engineer Bob Kessler Darell Doty and Bob Murphy engineering technicians.

Of course this effort did not start in a vacuum Some of us had an opportunity to learn about monitoring in both Drs A Parmelee s and M B Sterman s laboratories We are indebted to them and other investigators who had previously done physiological monitoring of infants Guidelines from "A Manual of Standardized Terminology Techniques and Criteria for Scoring of States of Sleep and Wakefulness in Newborn Infants" were followed Finally the computer staff especially Mr Jerry Mason and Mr Doug Hockin provided valuable feedback

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APPENDICES

Appendix I *Signal log*

Name
Shift 1 and
Shift 2 and
Starting (time) (footage)

Please write dow any problems otherwise O K it
Please enter set number being used

Time	Time code	EEG L	EEG R	Eye	EMG	S.A	Imp. resp	Ther resp	pCO_2	Resp tach.	Temp.	EKG	B-B	Cardio. tach.	Comments
1900															
2000															
2100															
2200															
2300															
2400															
0100															
0200															
0300															
0400															
0500															
0600															
0700															
0800															

End (time) (Footage) Comments

Name	Birth date	Date	Apgar
PF no baby	Birth eight	Onset of monitoring	Mother/Newborn/Infant
F no mother	Wks of gestation	Sex	Delivery

Appendix 2. *Feeding and infant care log*

AMT = Amount DUR = Duration

	Feeding				
Time	AMT	DUR	Diaper change	Humidity	Comments

Appendix 3 *Grass polygraph Amplifiers 1 through 8 (infant recording)*

			Gain					
Channel	Use	1/2 Amp Low freq	Scale	Sens	Filter	1/2 Amp High freq.	High freq. Pens	Filter
1	Time code	1	μV	15	in	1	60	in
	EEG	1	μV	7.5	in	1	60	in
3	EEG	1	μV	7.5	in	1	60	in
4	EM	0.3	Variable		in	0.1	60	in
5	EMG	10	μV	3	in	1	90	in
6	S.A	1	mv	75/90	in	1	60	in
7	Imp. resp.	0.3	mv	Variable	in	0.1	30	in
8	Nasal thermistor	0.3	Variable		in	3	90	in

Choose mV/cm or μV/mm settings and appropriate sensitivities depending on the signal.

Appendix 4 *Suppliers and brand names*

1. Chest electrodes, pregelled and disposable no. 65375-100 by American Hospital Supply Santa Ana, California 92705
2. Extension connectors KDC connecting wires no. 65356, by American Hospital Supply Santa Ana, California 92705
3. Skin Temperature Sensor (YSI) by VWR Scientific Yellow Springs, Ohio
4. Hypoallergenic Tape, no 1533 Micropore Skin Tone Surgical Tape One Inch by the 3M Company
5. Beckman Electrode Paste by Electronic Instrument Division, Beckman Instrument Inc Schiller Park, Illinois 60176.
6. E5S Silver Cup Electrodes by the Grass Instrument Company Quincy Massachusetts, 02169
7. Transpore Surgical Tape One-Inch by American Hospital Supply Santa Ana California 92705
8. Kerlix Roll, no. 6715 4 1/2 Inch, 6-ply roll, Kendall Hospital Products Division.
9. Grass Electrode Cream by the Grass Instrument Company Quincy Massachusetts.
10. Size 8 French Feeding Tube Infant, Pharmaseal no. K 31 by the American Hospital Supply Santa Ana, California 92705
11. Thermistor Bead (Tenwal GB 32J*) by Newark Electronics Company Inglewood, California 90304
12. Teflon-insulated wire, 28 a.w.g. by Newark Electronics Company Inglewood, California 90304
13. Somatic Activity Electrodes, assembled by the SIDS Project engineering staff (page 22 of this manual).
14. Coated coaxial cable, teflon, by Cooner Wire Company Chatsworth, California 91311
15. Differential amplifier 7P 511F by the Grass Instrument Company Quincy Massachusetts.

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(A list of earlier supplements can be obtained from Almqvist & Wiksell Tryckeri AB, Uppsala, Sweden without charge.)

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Exploring Child Health and its Ecology

The Kirkos Study in Addis Ababa

An evaluation of procedures in the measurement of acute morbidity and a search for causal structure

By LENNART FREIJ and STIG WALL

ALMQVIST & WIKSELL PERIODICAL COMPANY STOCKHOLM SWEDEN

EXPLORING CHILD HEALTH AND ITS ECOLOGY

The Kirkos Study
in Addis Ababa
–
an evaluation of procedures
in the measurement of
acute morbidity
and a search for
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A report from a study jointly
undertaken by

The Ethiopian Nutrition Institute

The Ethio-Swedish Paediatric Clinic
Department of Paediatrics
University of Addis Ababa

The School of Social Work
University of Addis Ababa

The Public Health Department
Municipality of Addis Ababa

From the Department of Statistics, University of Umeå, Sweden,
the Department of Preventive and Social Medicine, University of Umeå, Sweden
and the Department of Infectious Diseases, University of Göteborg, Sweden

EXPLORING CHILD HEALTH AND ITS ECOLOGY

The Kirkos Study in Addis Ababa

–

an evaluation of procedures in the measurement of acute morbidity and a search for causal structure

by

LENNART FREIJ
Physician at the Ethio-Swedish Paediatric Clinic, Addis Ababa, 1969–1973.
At present Physician at the Dept. of Infectious Diseases,
University of Göteborg, Sweden.

STIG WALL
UNESCO Associate Expert, Statistical Training Centre, University of Addis Ababa, 1972–1973. At present Research Associate in Applied Statistics, Dept. of Preventive and Social Medicine and Dept. of Statistics, University of Umeå, Sweden.

The Ki ko tudy was j intly ganized by the Ethiopian Nutrition Instit the Ethio-Swedish Pediat ic Clini the School f Social Wo k f the Unive ity f Addi Ababa nd the Public Health Depart ment f the Muni ipality f Addi Ababa The data collection and the initial valuation wa carried out in Addi Ababa in 1972 73 and in 1974 75 The continued analy i has mainly been pe f rmed in Swed The pa ti ipatio f Yemane Kidane (Ethiopian Nut ition Institut) nd GB an St ky (Directo f the Ethio-Swedi h Pediatric Clini 1970-73) has been sential f the ontinuity f this ll bo ti esear h ff t They have given important cont ibu- ti ns i the work l ading t thi epo t

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LIST OF NOTATIONS

T	total illness
G	gastroenteritis
R	respiratory illness
O	"other" illness
D	illness episode duration
H	"health" episode duration
M	frequency of illness episode occurrence
γ_D	recovery propensity parameter
γ_H	illness susceptibility parameter
μ_D	mean duration of illness episode
μ_H	mean duration of health episode
f( )	frequency function
F( )	distribution function
E( )	expected value of
V( )	variance of
P( )	probability of
$(\hat{\ })$	estimated value of
$(\bar{\ })$	sample mean of
s^2	sample variance
n_C	number of children
n_h	number of household
n_E	number of episodes
$\hat{p}_j$	estimated individual morbidity
$\hat{p}$	estimated group morbidity
P_j	true individual morbidity
P	true population morbidity
Tr	*the event of episode truncation*
L	length of home-visit observation period
ℓ	*space between home-visits*
v	number of home-visits
ν	home-visit order number
C_j	correction term for dependent *longitudinal observations*
exp( )	exponential function of
P_O	observed proportion of individual *morbidity*
P_R	recalled proportion of individual morbidity
MSE	mean square error
MSI	mean square inconsistency
AID	Automatic Interaction Detector
BSS	between group means sum of squares
TSS	total sum of squares
RSS	sum of squares due to linear regression
BRSS	between groups regression sum of squares
p_{ij}	path coefficient expressing the direct potential causal effect of variable j on variable i
r_{ij}	correlation coefficient between variables i and j

CONTENTS

INTRODUCTION

The promotion of child health is a major priority to health workers and planners in most developing countries characterized by large child populations in which infectious diseases and malnutrition in principle preventable conditions are highly prevalent The basic problem is how to achieve an optimal use of meagre resources in terms of manpower and economy for the maximum benefit to the great masses of children The main objective of an Ethiopian community research project (m) carried out in 197 73 and in 1975 was to contribute to the understanding and also towards the solution of this vast problem This paper is one of a se ies of reports from this project Its aim already stated in a preliminary report (m) is to evaluate a measure of acute morbidity one important indicator of child health and to analyse variations in this measure in relation to socio-environmental and individual background factors

The necessity of viewing child health as an ecological phenomenon in a complex system of interrelated medical and socio-environmental factors is emphasized in recent medical literature (m m m m) Community based surveys taking a multifactorial approach in the assessment of d terminants for child health (m m m m m m m m) are however scarce of limited scope and often fail to consider the multivariate nature of the problem in the analyti al phase of data processing

Sim l conclusions reached t the technical discussions of the World Health Assembly in 1974 (m) recogni e the importance for organi ers of health serv ces to conside all the environmental factors that influence health lling for a multidisciplinary approach based on close cooperation between health and social services which lso may imply non-medical solutions to medical problems It was also pointed out that shortage of infor mat on is a centr l problem in this field More basic demographic data detailed information on socio-economic conditions as well as accurate mortality and morbidity data would be needed for an adequate analysis of the interplay of social psychological cultural economic and biophysical factors as agents i the etiology of disease in the assessment of health needs and priorities and for the ev luation of health programs To achieve

this reliable and valid indices as well as appropriate survey instruments would also have to be developed

This broad approach in the study of child health was also implicit in the present study from the beginning - even if its scope was considerably limited for various practical reasons The basic assumption was that factors determining child health are to be found in the socio-environmental as well as in the health service sector This led to the organization of a socio-medical statistical research team from local institutions in Addis Ababa and the organizing of surveys of socio-economic and health conditions in a typical area of the city at the same time as the performance and the community utilization of a small MCH clinic was studied

The literature on child health in developing countries provides results that are relevant for the choice of variables in a community child health study but offers very little theoretical and methodological guidance for the formation of definitions and measures of the central components in a child health system. Thus with regard to the central concept of child health no widely accepted definitions or general measures are available The emphasis in the literature on the high prevalence of infections and malnutrition among children in developing countries indicates however two important aspects of child health The synergistic interaction between infection and malnutrition (79) was for instance taken as the basic hypothesis in a Guatemalan community study (80) which indicated that food supplementation had a positive effect on children s weight development as well as on the rate of infections A high load of acute illnesses especially diarrhoeal diseases was also shown to be associated with impaired childhood nutritional development in another study undertaken in Guatemala (81) Evidence of this relationship is also increasingly to be found in the immunological literature (44 78) Especially with regard to cell-mediated immunity malnutrition leads to a deterioration of the body s immune functions causing decreased resistance to infections which also will become more severe and lead to further impairment of the nutritional status due to decreased food intake and other mechanisms

It was therefore natural to choose measures of the load of infectious illnesses here considered under the term acute morbidity" and nutrition as the two major indicators of child health in this study Uncontroversial and easily interpretable definitions and measures feasible for application in community surveys are however not available for either of these com-

ponents especially not for morbidity The present publication which is devoted to the analysis of morbidity will therefore start with a review of the conceptual problems and of different approaches in the measurement of morbidity as a background to the measurement procedures chosen in the Kirkos study These will then be evaluated in terms of the statistical properties of the resulting measure Finally variations in this morbidity measure in relation to socio-environmental and individual background factors will be analysed by multivariate statistical methods The results will serve as basis for a further discussion about the causal structure

CHAPTER 1

APPROACHES IN THE STUDY OF MORBIDITY

1 1 CONCEPTIONS OF HEALTH AND ILLNESS

Recent reviewers of measures and indicators of health agree that tradition al measures of mortality and morbidity would no longer be a satisfactory basis for the rational planning and evaluation of health programs in indus trialized countries (s m m m m) The gradual decrease of mortality rates and the increase of life expectancy noted especially in the younger age groups in the industrialized countries during the first half of this century have levelled off and further gains are likely to be modest unless there are important break throughs in the prevention of chronic disease and accidents (m) This stability does not imply that no changes in health take place but illustrates the need for more sensitive health indices tak ing account of the social and economic consequences of illness as well as the quality aspects of life WHO gives a positive definition of health "Health is a state of complete physical mental and social well-being and not merely the absence of disease and illness" Attempts to form general health indices based on this positive concept of health have however met with many constraints as it is difficult to combine clear definitions with a high degree of reliability and validity of a measure which must also be operationally feasible for use in population surveys

The concept of health is an abstraction and may be seen as comprising many components biological physiological social etc which may each have a 'healthy-unhealthy' dimension Sullivan (m) states that there is little justification for the assumption that a unidimens onal continuum underlies and relates the measures referred to as healthy and unhealthy in different contexts Health defined without reference to a specific situation or pur pose of measurement may be merely a verbal artifact' Attempts to create health indices for general application have therefore been rather pragmatic in their approaches mainly focusing on the measurement of the outcome of illness Sullivan (m) for example proposes a measure based on the degree of disability in disease or injury as reported at interviews providing the respondant with an objective frame of reference for the description of his disability in terms of how it limits his ability to carry out 'his major

activity" He also suggests that this measure can be combined with a measure of mortality but does not detail the mathematical aspects of his proposal

Another example of a general health measure is that suggested by Fanshel and Bush (43) who construct a unidimensional index based on different health aspects They describe 11 levels from optimal well being to coma and death but are then faced with the problem of assigning weights to each of these levels A similar but more refined description of functional states is given by Patrick et al (37) This is based on three functional scales physical activity mobility and social activity These scales are combined and weights are assigned by a panel of medical and non-medical judges They suggest this instrument for use in household interviews which may however present the problem of respondant recall

Chiang and Cohen (34) present a stochastic approach to developing an index f health which is based on the average duration spent in health states by an individual over a year and suggested for use with regard to empirical data from sample surveys They recognize that health is a dynamic phenomenon varying on a continuum from optimum well-being to extreme illness and divide thi into ordered sets of health states Transition probabilities from one state to another are expressed in terms of intensity functions The proposed index which is equivalent to the fraction of the year a person is healthy varies from zero to null However their reasoning is entirely theoretical and health is not defined in any concrete way They propose on the other hand that the model can be used for different definitions of health One difficulty is that weights have to be assigned to the different states which implies a unidimensional view on health as well as an element of subjecti judgement The fact that time lost by mortality is equated with time spent in illness may also increase the difficulties to interpret this index

The efforts to create general health indices in industrialized countries lthough none of these have so far been widely accepted or tested in empir al situat ons are not parallelled by a similar search for methods of assessing health status in the developing countries (40) Furthermore the d scussion on health indices is cent red on the health of adults No atten t on seems to have been paid to the speci l problems in forming a general inde of health for children The objections to the use of health indices based on mort l ty rates and life expectancy are less relevant for the

situation in developing countries (10) Here mortality especially in childhood has a more uniform background of infection and malnutrition which can be reduced by preventive measures These countries however often lack functioning systems for the notification of deaths and births It would probably also be justified to suggest that information about the illness leading to death would be a more sensitive indicator of child health than mortality rates Measures of morbidity would reflect more of the quality aspects of life and would in addition also be more suited to sample survey techniques

A measure of health for children in a developing country could incorporate components such as physical social and emotional well-being The previous discussion has however emphasized the difficulties in creating a combined index of health both in terms of interpretability and feasibility It has already been indicated in the introduction that in an exploratory study of the present kind it was natural to concentrate on the common problems of infection and malnutrition in the attempt to develop measures of health Clinical experience indicates that infection often presents a short term problem whereas malnutrition is a more chronic state of ill health A general index of morbidity combining these aspects would probably have to be based on some measure of their functional and social consequences This would then lead to the same conceptual and practical problems as discussed above especially if such an index were to be applied to children of different age groups In this situation we have therefore chosen to analyse the acute and the chronic illness problems separately This paper is concerned with the occurrence of acute morbidity which in spite of several limitations can still be considered as an important measure of the burden of illness

1 2 ACUTE MORBIDITY SOURCES OF DATA AND MEASUREMENT PROCEDURES

Comprehensive and unbiased information on morbidity in a community can hardly be obtained from official notification of a few diseases or statistics from hospitals and clinics This is especially true in developing countries where these kinds of statistics are often only available sporadically Community surveys would be the only practical way of measuring the morbidity experienced in a given population Point prevalence figures obtained in cross sectional studies which are relatively easy to organize may yield valuable information about chronic conditions but would be in-

adequate in the study of acute illnesses of short duration If one wants to measure the pattern of acute morbidity both on an individual and aggregated level the study must necessarily have a longitudinal design The organiza tion of such studies is difficult being expensive as well as staff and time consuming The following review of some of the community based longi tudinal studies which present data on acute childhood illnesses underlines some of the conceptual and practical problems encountered in the measure- ment of morbidity A survey of the results of these studies is also given in Table 7

• Fields covered by previous research

Many morbidity studies have focused their interest on specific conditions Since the 1920 s and onwards several studies covering periods of 1 3 years, have dealt with the occurrence of respiratory illnesses in various communi ties Some of the earliest studies of this kind were carried out by Volkenburgh and Frost (44) among Baltimore families and by Collins and Gover (45) among college students and families of medical officers in the USA In the 1940 s Tucher (46) studied incidence rates in some rural com- munities in the USA Incidence rates and intra-household spread of infec tions were investigated among families of Canadians attached to a medical faculty by Buck (47) in rural England by Lidwell and Sommerville (48) and among working class London families by Brimblecombe et al (49) McCammon (50) presents data on respiratory infections from a long term health study carried out in 1926-1966 among middle class urban American families A six year study (51) undertaken more recently in a similar community gives inci dence figures and microbial etiology of respiratory diseases Those studies document the importance of the age factor for the rate of respiratory infec tion The highest incidences are universally found in the younger age groups

Whereas diarrhoeal disease is widely documented as an important cause of childhood mortality (9 52) the natural history of this disease entity has less often been the single subject of longitudinal community investigations. Such tudies giving figures on the occurrence epidemiology and etiology of diarrhoeal disease are however reported by Gordon et al (53) Scrimshaw et al (54) Mata et al (55) Bruch et al (56) from rural Guatemala by Gordon t al (57) and Ghai and Jaiswal (58) from rural India by Lie et al (59) from urban Indonesia and by Higgins et al (60) from rural Egypt These studies indicate that diarrhoeal disease in developing countries is a major health problem especially during the weaning period

and is often associated with nutritional deficiency The incidence rises towards the end of the first year and remains at high levels during the second and third years of life whereafter if often declines dramatically

A broader approach in the study of childhood morbidity is found in the now classical studies carried out in Newcastle upon Tyne by Spence et al ([illegible]) and Miller et al ([illegible]) and in Cleveland USA by Dingle et al ([illegible]) in which illness experience in different age groups was investigated with regard to the quantitatively important respiratory and enteric infections as well as other conditions The predominance of respiratory and intestinal infections is also documented in extensive field studies from rural Guatemala by Scrimshaw and associates ([illegible]) and by Mata ([illegible]) from urban India by Feldman et al and Kamath et al (45 73) by Malhotra and Prasad ([illegible]) and Datta Banik et al (34) and from Costa Rica by James ([illegible]) Infant morbidity was studied in India by Poti and Biswas ([illegible]) and in Ethiopia by Dodge and Demeke (37) Recent figures on respiratory and enteric infections in industrialized countries are available in surveillance studies of viral infections carried out by Fox et al (47 48) in Seattle and New York

Incidence data on total illness given in some of these studies (34 [illegible]) may reflect the burden of illness but are not uniquely interpretable especially as duration and severity of illness are not taken into account Number of days of illness per year was reported by Malhotra and Prasad ([illegible]) and used by Martorell ([illegible]) as a measure of morbidity in a study of the relationships between acute illnesses and nutritional development in Guatemalan children A similar measure was used by Cravioto in a study of infant health and its background factors in rural Guatemala ([illegible]) In a longitudinal study of illness among Boston children *followed from birth to the age of 18 years Valadian ([illegible]) employed a central* measure of illness burden in which both duration and severity were considered The basic score of 1 was assigned to a respiratory illness with involvement of both upper and lower respiratory areas A corresponding basic score evidently based on clinical judgement was also used for other illnesses This value was then decreased or increased according to illness duration complications or severity as compared to the condition with the basic score of 1 The highest ratings were found in pre-school children This measure was demonstrated to be sensitive enough to discriminate between Nigerian children of different socio-economic classes in a study by Rea ([illegible]) None of these authors however document the objectivity and the reliability of the measure

• Design problems and their implications

Longitudinal community studies on morbidity may be retrospective or prospective or combine these designs Evidence of morbidity may be based on self reports by the studied subjects or members of their families collected at interviews or in other ways Evidence may also be sought in clinical observations laboratory tests etc which may sometimes be used to arrive at diagnoses to judge severity and complications or to study for instance the etiology of infections The collectors of morbidity data may be non-medical field workers or medically qualified staff Obviously the different designs have implications both for the validity and the reliability of the measure of morbidity

Self reported data may reflect illness and need of health care as perceived in the community and may be useful in situations where measures of morbidity will be used in the planning and evaluation of health care systems that involve the active participation of the society under study In retrospective studies this kind of subjective evidence of morbidity must be based on recalled data for various periods of time although the reliability would be affected by the memory factor

Morbidity observations by non-medical staff may lack in diagnostic accuracy What is gained in this respect by the use of medically trained observers may be outweighed by various forms of bias e g the tendency to judge illness in terms of therapeutic needs and possibilities As pointed out by Sullivan (ms) clinical evidence of illness is often selected from characteristics that are useful in the treatment of illness and other characteristics that are important to the individual or his society may be omitted Moreove clinical examinations may reveal conditions that are unnoticed by the individual Individuals may also vary in their subjective and behavioral responses to the same diseases On the other hand illnesses experienced by the individual may not be subjected to clinical classification Sullivan lso argues that whereas clinical examination procedures may be feasible in sample surveys for single specific purposes they cannot be extended to obtain meaningful measures of morbidity in general as clinical medicine has numerous diagnostic criteria but no widely accepted criteria of morbidity that could be readily measured in sample surveys

The lack of generally accepted procedures in the measurement of morbidity is also reflected by the variation in and the mixtures of designs found in

the studies reviewed above In most cases - for obvious practical reasons data collection could not be organized on a continuous basis One study used intervals of 3-4 days (48 73) in other studies the interval was one week (33 [illegible] 80 [illegible] 92 104 144) two weeks (17 28 31 34 81 93 [illegible] 111 118 120) one month (30 37 [illegible] [illegible] 136) or longer (83 108 143) Although most of the studies were prospective they often used recalled information from interviewees covering intervals of various lengths Some studies relied mainly on self reports (30 31 37 [illegible] 83 80 81 118 120 136,143) others combined this with some form of clinical or laboratory assessment at the regular contacts or as arranged when illness was reported (17 34 47 48 57 [illegible] [illegible] 92 104) In one case mothers were encouraged to take their children to a 'morbidity clinic' for examination in the event of illness (111) Other studies sometimes used information collected from general practitioners and hospitals to supplement data obtained in the homes ([illegible] [illegible] 127 143) In the studies carried out in Guatemala medical interference by the observers was actively avoided In some other studies medical advice and treatment were offered Primary data were sometimes collected by non-medical field workers (30 34 37 81 83 [illegible] 117 118 120) sometimes by doctors or nurses (17 28,37 48 [illegible] 73 [illegible] [illegible] [illegible] 92 143) Some reports do not specify which category of observers was used As in the Cleveland study (28) in which illness detection was based on a daily record kept by the mother checked in turn by nurses at weekly home visits and with all reported illness cases checked by physicians the majority of the studies did not rely only on one source of information Questions about the reliability and validity of these various approaches or their combinations have rarely been raised

In one of the Guatemalan studies Martorell (81) reports the 'sensitivity' of maternal reporting for diarrhoeal disease as 66 % and the 'specificity' as 99 % as compared with a physician s examination i e 66 % of those children whom the physician found to have diarrhoea were also reported by the mother and 99 % of those found free of diarrhoea were also reported so by the mother For respiratory disease the 'sensitivity' was 92 % and the 'specificity' 64 % Martorell also observed the problem of accuracy with regard to recalled information His results indicated 12 37 % under reporting when the recall period was two weeks in comparison with daily reports (See Chapter 4) Another study from Boston reported by Tager et al (127) not referred to above compared the efficiency in the detection of respiratory illnesses by means of home surveillance calls parent completed diaries and monitoring of school absence lists Of the totally discovered episodes 35 % were revealed by means of the parents daily records alone

and would have been missed on the home-visits that were undertaken as often as every two weeks Furthermore physicians records were not reliable enough to be used as the only source of data validation

The varying approaches and sources of information used in the morbidity studies reviewed above obviously imply substantial variations in both reli ability and validity and their results should therefore be interpreted and compared with caution

- Approaches of this study

This report is based on a prospective community study in which non-medical field workers collected morbidity data from mothers reports on their chil dren s health at the time of the home visits carried out every two weeks during one year The proportion of home visits on which the child was reported ill was taken as measure of illness load In order to evaluate the precision of this measure the necessary information on frequency and duration of illness episodes was collected during a smaller supplementary study Illness of some different categories are thus measured in this study basically only in terms of occurrence and duration and no attempt is made to include a subjective classification according to severity These deliberate limitations also imply that some of the mathematical approaches suggested by Chiang ([illegible]) to describe the distribution of time spent in various illness states would be applicable in this situation

Many of the studies reviewed above are mainly descriptive focusing on occurrence epidemiology and sometimes etiology of infections In some cases morbidity information is used to discuss the interrelations between nutrition and infection ([illegible]) Other reports discuss the associations between some socio-economic factors and morbidity ([illegible]) The complicated multivariate nature of this problem is however hardly reflected in the statistical analysis which is mainly based on bivariate tabulations Although of limited scope in several respects this study has the broad aim of exploring child health and its determinants as an ecological problem taking into account the multivariate nature of the problem both in the design of the study and in the analytical phase

CHAPTER 2

CONCEPTUAL AND FACTUAL FRAMES OF THE STUDY

2 1 THE RESEARCH STRATEGY

Structuring an applied research process involves clear definitions of the research problems and choice of study units and designs which in turn are clearly linked to the inferential ambitions of the study The Kirkos study aimed at an unprejudiced investigation of socio-environmental medical and health service factors in their determination of child health As it was realized that very little was known about the complex interrelationships between these factors and about methods for their identification and measurement it was appropriate to choose an exploratory research approach As described more in detail in another publication (#) this was seen as a process of inductive reasoning (Figure 1) starting with the identification of basic concepts as they are understood by the researchers and their arrangement as a conceptual model of child health The vaguely defined components in this model would then determine the choice of variables and the collection of data Data evaluation should include the identification of

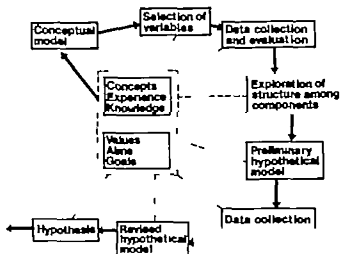


FIGURE 1 Th expl t ry res arch p oce

intercorrelations which may lead to the assumption of new components with new dimensions Some variables may have to be chosen as the closest expression for such components that may not be directly measurable by means of available data The further analysis may aim at the *identification of quantitatively important interaction patterns* between the variables which may lead to revisions of the original model assumptions In contrast to confirmatory studies in which pre-stated hypotheses are tested this kind of inductive research evaluates data with the intention of creating a sound basis for the generation of hypotheses as well as the building of methodologies and theories in the actual research field

It is within this frame of reasoning that we intend to discuss the measures of acute morbidity that were provided by the Kirkos project The aim of this chapter is to give a background account of the organization of the project describing the collection of morbidity data and the calculation of some basic measures of acute morbidity The next three chapters deal with the evaluation of the measurement procedures which also necessitated a smaller supplementary study The conceptual models of child health and of acute childhood morbidity are discussed in Chapters 6 and 7 as a basis for the further analysis of variation in morbidity in relation to several sets of socio-environmental and individual factors The use of multivariate statistical methods in the identification of interaction patterns precedes a tentative assessment of the causal structure and a revision of the original models

2 PROJECT DESCRIPTION

The area (Kirkos) chosen for the project was a densely populated part of a district in Addis Ababa A large proportion of the families were underprivileged lacking adequate housing and sanitation No local medical facilities were available Six houndred households were interviewed in February 1972 with regard to demographic and socio-economic conditions hygiene and sanitation education and cultural background At the same time a low cost Mother and Child Health (MCH) clinic was established in the area The households represented 2926 individuals 1534 of whom were children below the age of 15 years The 292 families that had children under the age of 7 years were selected for a longitudinal study which was started in March 1972 Fortnightly home visits were paid to these families during one year to obtain information on the morbidity and weight development of the 749 children originally present in these households A cross sectional study on the

prevalence of intestinal parasites was also performed A follow-up study aimed at all the original families was undertaken after one year to collect data on mobility changes in family composition and also on utilization of the MCH clinic A detailed description of the survey procedures the variables chosen and the primary data is given in another publication (81)

2 3 DESIGN OF THE MORBIDITY STUDY

Morbidity data were collected at fortnightly home-visits by a group of sociology students who had no previous medical training These non-medical field workers established good relations with the members of the households in spite of the fact that they did not volunteer medical or nutritional advice or any form of treatment If this was requested by the mothers they could however refer to the MCH clinic The use of medically trained staff - practically impossible to arrange due to shortage of medical professionals would have meant more detailed information about illnesses in terms of diagnosis severity etc On the other hand this arrangement would also probably have meant greater interviewer bias as well as considerable inter ference in medical and health matters as a medical professional can hardly abstain from action for ethical reasons on the discovery of ill health The use of non-medical observers was therefore considered to have two advantages active medical interference was avoided which was considered to be ethically justified as the families were given access to a new local MCH clinic, and uniformity with regard to basic notification of symptoms and illnesses d be expected from the interviewers

Children were recorded as ill or not ill on the day of each home-visit according to the mothers s report No questions were asked about the health development since the previous visit The home visitors naturally often saw the children, but did not undertake any clinical assessment If the child was reported as ill the main symptoms were recorded

The classification of illness into the main groups of gastroenteritis respiratory disease and 'other illness" was based on the individual records and carried out at a later stage by one carefully instructed person If the only symptoms were vomiting and/or diarrhoea (a history of at least 4 loose stools or at least one watery or bloody stool per day was considered as diarrhoea) the condi was classified as gastroenteritis Any symptom of sore throat cough or breathing difficulty was considered to constitute a

respiratory disease even if vomiting or diarrhoea were present The same classification was made if symptoms and signs of eye infection or ear in fection were combined with respiratory symptoms Otherwise these symptoms were considered under other illness' as was fever weakness abdominal pain skin infection etc Sometimes the presence of several symptoms may have been evidence of multiple infections but for the present study only one classification was made In a few cases in which the above rules were not applicable the condition judged to be most important was considered For each group of children the proportion of the total number of home-visits on which illness was recorded was taken as a measure of the total load of illness during the study period

2 4 INITIAL RESULTS AND AREAS FOR FURTHER EVALUATION

The basic measure of acute morbidity obtained from the one-year prospective study namely the proportion (p) of home-visit days on which illness was recorded for individual children (p_j) and for groups of children (p) can be regarded as an estimator of illness load in terms of time spent in various illness states

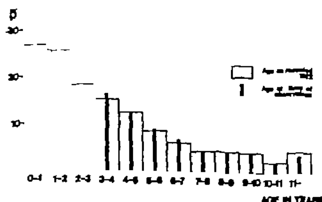


FIGURE 2 A ag morbidity $\bar{p}$ (tot l ill-ness) by ge group (Source: Table A1)

The age distribution of the 749 children by p is given in Figure 2 As all children did not complete the 26 fortnightly observations during the study year (Figure 28) p is based on p_j values weighted by the number of home-

visits completed for each individual child The highest values are found in the youngest age groups followed by gradually decreasing values in older children A longitudinal study design means that age is not a static factor The multivariate analysis in this study will however require that the same classifications are retained for individual children during the study period The age classification is therefore based on age as recorded at the baseline study (unless otherwise stated) This implies however that the resulting distribution of p by age (Figure 2) does not reflect the declining morbidity in each age class as the children grow older during the study year Consequently the somewhat more pronounced age differences with regard to p resulting from an age classification based on the individual child s age at the time of each observation would be a better estimation of the true distribution of morbidity by age (Figure 2)

This basis for the age classification is also used in Figure 3 which displays the relative contributions to p (total illness) by the various subgroups of illness The high morbidity in the age group 0-2 years is obviously mainly due to the high rate of gastroenteritis

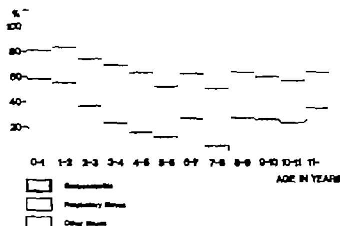


FIGURE 3 P rcentag distribution f ub las s of illne observ ti ns by g (Ag las ifications a based on ag t time f home-visit t individual children Sou Tabl A1)

As p is an estimator of time spent in illness by an average child the product of p and the corresponding number of children in each age group would estimate the quant ty of illness suffered by each age group over a period of time Figure 4 compares the percentage distribution of total time spent

in illness and sub-groups of illness (p group size) in 4 age groups with the percentage distribution of the number of children by age group It is interesting to note that in spite of constituting only 18 % of the total number of children the age group 0-2 years is responsible for more of the total time spent in illness due to diarrhoea than the other age groups together

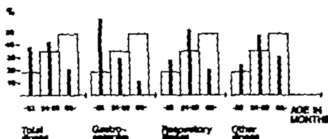


FIGURE 4 Percentag di trib ti f t tal time spent in different states f illnes by children in th se age group (black ba s) compa d with pe centage di tribution of number of children in each ge group (pen bar) (Sourc : Table A1)

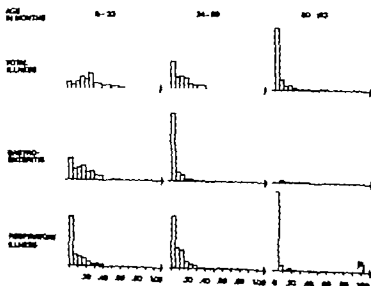


FIGURE 5 Di trib tion f the number of child en according t indi idual morbidity (p_j) by age (Source: Tabl A2)

An alternative approach in the description of the relation between morbidi ty and age is taken in Figure 5 It gives the distributions of the number of children in different age groups according to their individual morbidity values (p_j weighted by the number of home-visits) The proportion of chil dren with high p_j values gradually decrease with age especially in the case of gastroenteritis Figure 6 finally gives a complete documentation of all the individual relationships between morbidity and age in the form of scattergrams of p_j (weighted by the number of home-visits) by age

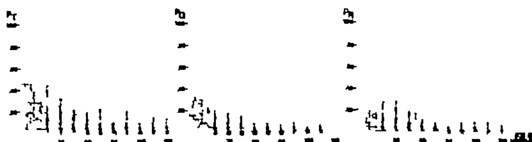


FIGURE 6 Scattergrams of individual morbidity (p_j) by ge

This presentation of the outcome measure of morbidity obviously reveals that large variations are due to the age factor A more detailed analysis of variation with regard to all criterion variables must however be preceded by an evaluation of the measure employed in this study to determine to what extent and in what circumstances it is a good estimator of illness load for individual children and for groups of children with regard to ill ness in general and specific groups of illness

The accuracy of the morbidity measure may be affected by the sampling methods Thus the fact that the sampling unit was the household and not the individual child would induce correlations between children in the same household Observer bias is another possible source of inaccuracy The proj ect did not provide the means for an analysis of observer bias but there is no reason to believe that this would be of a systematic nature Respondent bias would depend on the mothers cooperation and accuracy in reporting about their children s illnesses When dealing with self reported data this is however conceptually a complex problem which by definition would probably not be available for analysis Inaccuracy due to faulty memory was however avoided in this study as no recalled information was used (Chap-

ter 5) Other sources of inaccuracy may have been caused by the method of sampling observations over time as the precision of the measure would depend on the design of the survey its duration and the degree of incompleteness This is the main topic of the statistical evaluation of the measure of morbidity in the following chapters which also discuss a supplementary study of frequency and duration of illness episodes This also forms the basis for the concluding analysis of variations in morbidity in relation to all the variables included in the model

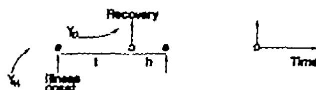
CHAPTER 3

PATTERNS OF ILLNESS OCCURRENCE

3 1 THE PROCESS

The approach employed in this study to the measurement of morbidity gives information as to whether the individual child is in a certain state of health at equidistant intervals along the time axis As a measure of his illness load we have taken the proportion of the observation occasions on which the individual was observed ill

The evaluation of the goodness of this measure involves the postulation of models which incorporate existing theoretical knowledge and may even call for further empirical data about the underlying pattern of illness occurrence *As it is impossible to obtain full knowledge about all the links in* the causal chain leading to illness it is natural to regard the pattern of illness occurrence over time as a stochastic process made up of illness *episodes* that may be described according to their *frequency* and *duration*.



From the statistical point of view illness occurrence can be seen as an "alternating renewal process (38) where the illness state' of length D=t and 'health state' of length H=h alternate as illustrated above The basic assumption behind this model is its lack of 'memory' in the sense that given illness onset or recovery the subsequent development is not dependent on previous illness experience It should be noted of course that the model is applicable only to regenerative states Thus it is for instance not valid in the case of measles

The sequences $\{t_1\ t_2\ \ \}$ and $\{h_1\ h_2\ \ \}$ of "illness" and "health" episodes respectively thus define an alternating renewal process with density functions $f_D(t)$ and $f_H(h)$ being in a logical sense models of "recovery propensity" with parameter γ_D, and *illness susceptibility* with parameter γ_H In consequence they will both be related to $P(M=m)$ the probability that the child will experience m illness episodes during a certain time interval

If μ_{jD} and μ_{jH} denote mean duration of "illness" and "health" episodes respectively for the j^{th} child then the child after a large number of episodes will have spent a proportion of time

$$(t_1\ t_2\ \ )/[(t_1\ t_2\ \ )\ \ (h_1+h_2\ \ )] \sim \mu_{jD}/(\mu_{jD}+\mu_{jH}) = P_j$$

in the illness state It can be proved (*) that independently of the form of $f_D(t)$ and $f_H(h)$ if $P[x(t) = 1]$ denotes the probability that at t the child is in state "1 = "illness" then

$$\lim_{t\to\infty} P[x(t) = 1]\ \ \ \mu_{jD}/(\mu_{jD}+\mu_{jH})$$

the "equilibrium" solution For an empirical illustration see Figure 20

The total load of illness for individuals $(P_j\ \ j\ \ 1\ \ ,n_c)$ and groups of children (P) assuming equal number of home-visits per child will be estimated by

$$P_j\ \ \sum_{i\ 1}^{v} x_{ij}/v \quad \text{and} \quad P\ \ \sum_{j\ 1}^{n_c} P_j/n_c \quad \text{where}$$

$$x_{ij}\ \begin{cases} 1 & \text{if child no}\ \ j\ \text{is observed ill on home-visit no}\ \ i \\ 0 & \qquad\qquad j\ \ \text{not}\ \ "\ \ "\ \ "\ \ "\ \ i \end{cases}$$

n number of children
v number of home-visits

In view of the fact that an index of morbidity so defined is composed of in a multiplicatory manner frequency of episodes M and their mean duration $\bar{D}$ a special study of these two components was found necessary The

statistical properties of their probability distributions are rarely discussed in medical literature and when this has been done (22) attempts at verifying theoretical models on empirical data have been of limited scope To the best of our knowledge development research in the field of health has not considered the model-building aspect in the analysis of illness occurrence and cannot consequently benefit from it as a tool in the planning and evaluation of health programs

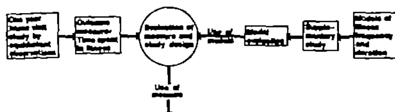


FIGURE 7 St ps in g ner ting and evaluating the measur f illnes load used in thi study

The theory of stochastic processes i e realizations of systems developing in time or space in accordance with probabilistic laws has found increasing application by providing mathematical models for a wide range of social and epidemiological phenomena (7 23) Since mathematical models serve as simplified descriptions of what are often complex realities they necessarily involve some more or less plausible assumptions In the present study the suggested models will be evaluated by means of data from a small scale supplementary study (Chapter 4) and serve as tools for the evaluation (Chapter 5) of our illness load measure generated from the one-year study (Figure 7)

3 2 EPISODE FREQUENCY

Let us first consider the behaviour of the random variable $M(t)$ the number of illness episodes occurring to an individual during the time interval (0 t) The probability distribution

$$P_m(t) \quad P[M(t) \quad m|M(0) = 0] \qquad m = 0\ 1\ 2$$

is the probability that a randomly chosen child will experience m episodes during (0 t) and is also an idealization of the proportion of children in the population having m illness episodes

Let the probability that an episode will occur in a time interval $(t \quad t+\Delta t)$ be $\gamma_H \, \Delta t \quad o(\Delta t)$ where $o(\Delta t)$ is a standard notation referring to any function of Δt that tends to 0 faster than Δt itself γ_H thus denotes the individual child s *constant susceptibility* to illness which in $(t \quad t \, \Delta t)$ is assumed to be *independent of previous illness experience in $(0 \quad t)$* Also the probability of more than one episode in $(t \quad t+\Delta t)$ as $\Delta t \rightarrow 0$ is assumed to be of the magnitude $o(\Delta t)$ and is thus negligible

A commonly used model for the occurrence of "random" and "rare" events within fields like accidental research haematology and isotope counting is the simple Poisson process It has also been suggested by Chiang (21) as a basic model for the construction of an index of health

We may start by letting the single Poisson distribution

$$P_m(t) \quad (\gamma_H \, t)^m \quad \exp(\gamma_H \, t)/m \qquad m = 0 \; 1 \; 2 \qquad (3 \quad 1)$$

describe the rate of illness episode occurrence for an *individual* child with susceptibility' parameter γ_H.

There are however two crude assumptions underlying this model

that illness episodes are of negligible durations
that illness susceptibility remains constant within as well as between children

Consider the first of these two assumptions Since (3 2 1) is based on the assumption that illness episodes are free to operate in an empty system it does not recognize the system as being composed of two alternating states Let $P_{ij}(t)$ denote the probability that an individual during $(0 \; t)$ will experience i illness" and j 'health *episodes Then*

$$P_m(t) \quad P_{mm}(t) \quad P_{m,m+1}(t) \qquad (3 \; 2 \; 2)$$

and

$$P_{mm}(t \; \Delta t) \quad P_{mm}(t)(1 \; \gamma_D \Delta t) \quad P_{m-1,m}(t)\gamma_H \Delta t \quad o(\Delta t) \qquad (3 \; 2 \; 3)$$

This means that equally many (m) "illness and health episodes in (0 t Δt) can occur in either of three ways

they all occur in (0 t) and the child remains ill with probability $1 \ \gamma_D \Delta t$ in (t t Δt)

the m^{th} illness episode occurs with probability $\gamma_H \Delta t$ in (t t Δt)

two episodes occur with probability o(Δt) in (t t Δt)

In the same way

$$P_{m\ m+1}(t \ \Delta t) = P_{m,m+1}(t)(1 \ \gamma_H \Delta t) \quad P_{mm}(t)\gamma_D \Delta t \quad o(\Delta t) \qquad (3\ 2\ 4)$$

(3 2 3) and (3 2 4) lead to the differential equations

$$P_{mm}(t) = - \gamma_D \ P_{mm}(t) \quad \gamma_H \ P_{m-1\ m}(t)$$

and (3 2 5)

$$P_{m\ m+1}(t) = \quad \gamma_H \ P_{m,m+1}(t) \quad \gamma_D \ P_{mm}(t)$$

which can be solved explicitly with the initial conditions

$$P_{01}(0) = 1 \quad P_{11}(0) \quad 0$$

Thus

$$P_m(t) = P_{mm}(t) + P_{m,m+1}(t) \quad \gamma_H[P_{m-1\ m}(t) \quad P_{m,m+1}(t)] \qquad (3\ 2\ 6)$$

(3 2 6) is intuitively interpretable as the net rate of occurrence of the m^{th} episodes at time t

In particular when $m = 1$

$$P_1 = \gamma_H[P_{01} \quad P_{12}]$$

is the rate f first occurrence

The moments of the number of renewals e g expected value and variance of the number of episodes in (0 t) could be derived from the theory of renewal processes

Considering the second assumption underlying the model in (3 2 1) it is obvious that certain children contract illness more easily than others and that $P_m(t)$ should actually be interpreted as a conditional distribution

$$P_m(t) \quad P[N(t) = m \mid \gamma_H]$$

It is reasonabl however to hypothesize that the simple model in (3 2 1) may suffice to characterize episode frequency also in groups of children at least fairly age-homogeneous ones age being a priori a logical stratifi cation variable accounting for substantial variation This variation may however also be accounted for by reinterpreting the 'parameter' γ_H as having a probability distribution of its own with density $g(\gamma_H)$

Some experience could be gathered from other authors incorporating variabil ity in risk in their applications of stochastic processes to sickness and accident statistics (a zz aa az) They successfully put the frequency function of λ equal to a gamma distribution which has proved to be a flexible model capable of describing patterns of variability It is specified by

$$g(\gamma_H) \quad \beta^{\alpha} \quad \gamma_H^{\alpha\ 1} \quad \exp(\ \beta\ \gamma_H) \ /\ \Gamma(\alpha) \qquad \gamma_H \quad 0 \quad \alpha \quad \beta \quad 0$$

where the gamma function $\Gamma(\alpha)$ is defined by

$$\Gamma(\alpha) \quad \int_0^{\infty} y^{\alpha\ 1} \exp(-y)dy$$

The distribution of episode frequency will be a *compound* Poisson distribution where the susceptibility distribution $g(\gamma_H)$ is used as weights

$$P_m(t) \quad \int_{\gamma_H} P[N(t) \quad m|\gamma_H]g(\gamma_H)d\gamma_H = \frac{\Gamma(m+\alpha)\beta^{\alpha}t^{m}}{\Gamma(\alpha)m.(t+\beta)^{m+\alpha}} \qquad (3\ 2\ 7)$$

Fo a unit time interval we have

$$P(N=m) \quad \frac{\Gamma(m+\alpha)\beta^{\alpha}(1+\beta)^{\ (m+\alpha)}}{\Gamma(\alpha)m} \quad \binom{m+\alpha\ 1}{m}\left(\frac{\beta}{1\ \beta}\right)^{\alpha}\left(1 \quad \frac{\beta}{1+\beta}\right)^{m} \qquad (3\ 2\ 8)$$

$$m = 0\ 1$$

This means that equally many (m) illness and "health" episodes in (0 t Δt) can occur in either of three ways

they all occur in (0 t) and the child remains ill with probability $1 \gamma_D \Delta t$ in $(t\ t\ \Delta t)$

the m^{th} illness episode occurs with probability $\gamma_H \Delta t$ in $(t\ t\ \Delta t)$

two episodes occur with probability $o(\Delta t)$ in $(t\ t\ \Delta t)$

In the same way

$$P_{m,m+1}(t\ \Delta t) \quad P_{m\ m+1}(t)(1\ \gamma_H \Delta t) + P_{mm}(t)\gamma_D \Delta t + o(\Delta t) \tag{3 2 4}$$

(3 2 3) and (3 2 4) lead to the differential equations

$$P_{mm}(t) = \quad \gamma_D\ P_{mm}(t) + \gamma_H\ P_{m-1\ m}(t)$$

and (3 2 5)

$$P_{m\ m+1}(t) = -\ \gamma_H\ P_{m,m+1}(t) + \gamma_D\ P_{mm}(t)$$

which can be solved explicitly with the initial conditions

$$P_{01}(0) = 1 \quad P_{11}(0) = 0$$

Thus

$$P_m(t) \quad P_{mm}(t) \quad P_{m,m+1}(t) = \gamma_H[P_{m-1,m}(t) \quad P_{m\ m+1}(t)] \tag{3 2 6}$$

(3 2 6) is *intuitively interpretable as the net rate of occurrence of the* m^{th} episodes at time t

In particular when $m = 1$

$$P_1 = \gamma_H[P_{01} \quad P_{12}]$$

is the rate of first occurrence

The moments of the number of renewals e g expected value and variance of the number of episodes in (0 t) could be derived from the theory of renewal processes

with acute morbidity the bulk of illness is obviously caused by infections The duration of an infectious illness may be seen partly as a function of virulence factors in the causing agent and partly as a function of host factors involved in resisting and combatting disease Varying duration ac cording to age may thus be explained by the specific etiological patterns and/or host factors characteristic of the different age-groups

Our objective then is to find an adequate expression for the probability distribution of D the duration of an episode

$$F(t) \quad P(D \leq t) \quad \int_0^t f_D(t)dt \qquad (3\ 3\ 1)$$

is the probability that the child will recover from an illness within a period of time t The survivor function

$$G(t) \quad 1 \quad F(t) \quad P(D \quad t) \qquad (3\ 3\ 2)$$

thus states the probability that the child will be ill for a period longer than t The density function $f_D(t)$ is related to the survivor function by

$$f_D(t) \quad -G\ (t) \qquad (3\ 3\ 3)$$

Considering a small time interval (t t Δt) and assuming that the chance of recovery within the interval is a function of t the duration of the episode attained so far and of Δt we define

$$\gamma_D(t) \quad \lim_{\Delta t \to 0} P[t \quad D \leq t\ \Delta t | D \quad t]/\Delta t \qquad (3\ 3\ 4)$$

where $\gamma_D(t)$ connotes the *"recovery propensity* the intensity with which *an episode of attained duration t will end Thus* the unconditional probability

$$P[t \quad D \leq t\ \Delta t] \quad P[t \quad D \leq t\ \Delta t | D \quad t] \quad P[D > t]$$

and

$$\gamma_D(t) \quad f_D(t)/G(t) \quad -G\ (t)/G(t) = \frac{-d \log G(t)}{dt}$$

Henc

$$G(t) \quad \exp\{-\int_0^t \gamma_D(\tau)d\tau\}$$

and

$$F(t) \quad 1 \quad \exp\{-\int_0^t \gamma_D(\tau)d\tau\} \tag{3 3 5}$$

with density

$$f_D(t) = \gamma_D(t) \ \exp\{-\int_0^t \gamma_D(\tau)d\tau\}$$

may serve as our general but still unspecified model of D This specification implies that adequate assumptions must be imposed about the behaviour of $\gamma_D(t)$

A constant rate of recovery $\gamma_D(t) \quad \gamma_D$ implying that the probability of the immediate termination of an episode does not depend on its "age" would yield

$$f_D(t) = \gamma_D \exp\{ \gamma_D \ t\} \tag{3 3 6}$$

i e an exponential distribution with expectation $\mu_D = 1/\gamma_D$ and variance $\sigma_D^2 = 1/\gamma_D^2$ where $\bar{D}$ mean observed episode duration estimates $1/\gamma_D$

A reasonable alternative model would be to retain the assumption of a constant rate of recovery within individuals but letting it vary in the population between children groups of children or sub-classes of morbidity i e by regarding γ_D as a stochastic variable with for example the distribution function $H(\gamma_D)$ Then

$$f_D(t) \quad \int_0^\infty \gamma_D \exp\{ \gamma_D \ t\}dH(\gamma_D) \qquad t _ 0 \tag{3 3 7}$$

defines a compound exponential distribution where we must specify the form of $H(\gamma_D)$ e g a gamma distribution (nn)

Situations frequently arise in practice when the time intervals between events in an alternating renewal process e g periods of "illness and "health follow *mixed distributions* where γ can take only discrete values $\gamma_1 \quad \gamma_k$ with associated probabilities $\pi_1 \quad \pi_k$ As a special case let us consider two types of illness e g acute/chronic occurring with probabilities π and $1 \ \pi$ and with durations described by $f_1(t) = \gamma_1 \exp\{ \gamma_1 t\}$ and $f_2(t) \quad \gamma \exp\{ \gamma_2 t\}$ respectively Then

$$f_D(t) \quad \pi\gamma_1 \exp(\ \gamma_1 t) \quad (1\ \pi)\gamma_2 \exp(\ \gamma\ t) \qquad (3\ 3\ 8)$$

defines a mixed two-term exponential distribution with

$$\mu_D \quad \pi/\gamma_1 \quad (1\ \ )/\gamma_2$$

and (3 3 9)

$$\sigma_D^2 \quad \pi(2\ \pi)/\gamma_1^2 \quad (1\ \pi)(1\ \pi)/\gamma_2 \quad 2\pi(1\ \ )/\gamma_1\gamma_2$$

From (3 3 8) and (3 3 9) it can be verified that the coefficient of varia tion is always greater than one and that the recovery propensity

$$\gamma_D(t) \quad f_D(t)/G(t)$$

$$[\pi\gamma_1 \exp(-\gamma_1 t) \quad (1\ \ )\gamma_2 \exp(\ \gamma_2 t)]/[\pi\exp(\ \gamma_1 t) \quad (1\ \pi)\exp(\ \gamma_2 t)]$$

decreases monotonically from

$$\pi\gamma_1 \quad (1\ \pi)\gamma_2 \quad \text{when } t \quad 0 \text{ to } \min(\gamma_1\ \ \gamma_2) \quad \text{when } t \to \infty$$

The mixed exponential distribution usually fits data better when a coeffi cient of variation greater than one is observed and a monotone decreasing recovery propensity is logically required the longer an episode lasts the more likely t is to represent a group of children or category of illness with low γ_D and thus we should have a decline in γ_D with time The mixed exponential distribution is also flexible in accounting for highly skewed distributions where well separated sub-groups can be identified

The two-term mixed exponential distribution contains three parameters to be estimated π γ_1 and γ_2 Usually this is done by an *a priori* defini tion of sub-groups where and 1 express their respective proportion-al size and γ_1 and γ_2 are estimated from each single exponential The mixed distribution then serves as a summarizing distribution Reversely the parameters can be estimated simultaneously from empirical data The obtained mixed distribution could thus be used to identify *a posteriori* interpretable sub-groups by letting duration of illness serve as a criteri on for discrimination (7 22)

An alternative interpretation would be to regard illness as developing in *two or more stages*. This would be justified from the clinical point of view in most infections which are often characterized by a prodromal stage, a *stage of maximum* intensity and a recovery phase. Let the number of such stages be k, the durations of which are independently exponentially distributed, each with the parameter γ. The total duration of an episode then follows a gamma distribution with the mean k/γ and the coefficient of variation $1/\sqrt{k}$. A generalization may also be allowed where the different stages are exponentially distributed but with different parameters $\gamma_1, \ldots, \gamma_k$.

If the latter interpretation were to be applied in practical field work, it would require medically trained interviewers and of course quite frequent home-visits. It would add information concerning one crucial assumption on which the above duration models are based — that of a *constant recovery propensity within individuals*. This is not of course a theoretically valid assumption but we still hypothesize that at our present state of knowledge and with the use of the present crude diagnostic and classification procedure, the simple exponential model suffices to describe episode duration within fairly age-homogeneous groups of children. We can also logically motivate the use of a mixed distribution to account for the heterogeneity in a sample of episodes which may represent etiologically different types of illnesses or different groups of children with varying illness susceptibilities and recovery propensities.

CHAPTER 4

FREQUENCY AND DURATION OF ILLNESS— a supplementary study

4 1 BACKGROUND AND SURVEY PROCEDURES

The main aim of this chapter is to test the theoretical models of illness frequency and duration discussed in the previous chapter This will be done empirically on an independently collected material from a supplementary study which unlike the one-year longitudinal study provides information about frequency and duration of illness episodes identified by observations made on daily home-visits

A second purpose is to identify and analyse practical and statistical measurement problems to which the studies reviewed in Chapter 1 pay little attention generally describing illness occurrence only in terms of mean incidence values Frequency distributions of the number of illness episodes are given only in one of these studies (ее ее) A few of these studies report on illness duration by mean values or give only summaric information about its frequency distribution (ꝡ ꝏ ꝏ ꝏ ꝏ-ꝏ ꝏ ꝏ)

The supplementary study was also intended to provide factual knowledge about illness frequency and duration which may be of general as well as local interest The patterns of acute morbidity among Ethiopian children are on the whole only documented by statistics from clinical institutions where visit and admission rates indicate the major role played by gastrointestinal and respiratory infections Community figures on illness occurrence in relation to age nutritional status and family income are however available from a study of rural children under the age of $1\frac{1}{2}$ years (ꝡ) The duration of acute illness does not seem to have been studied in Ethiopia The supplementary study described in this chapter may therefore also serve to fill a gap in local knowledge about incidence and duration patterns of illnesses in Ethiopian children

Distributions of frequency and duration of illness episodes are thus mainly described for different age groups and also in relation to other individual factors such as sex and nutritional status as well as to some household background factors In addition these data illustrate some aspects

of the spread of illnesses within the households

The survey was carried out over a 60 day period in February-March 1975 Care was taken to ensure that the same procedures were followed as in the one year survey (see 2 3) the only difference being that home visits were now made on a daily basis Thirty-eight households which had been included in the one-year study were identified in the section of the Kirkos area selected for this study Other households were selected at random from neighbouring houses until a manageable group ot 88 households with 53 children was obtained Three interviewers (two young school teachers and one sociology student) all without previous medical training were employed and instructed to carry out the home visits as described in 2 3 Thus daily information about the health of each child was obtained from the mother and recorded on the same type of protocols as used in the one-year study Each day the child was therefore classified as ill or not ill In case of illness the main symptoms were noted It was encouraging to find that the interviewers had no difficulties in being accepted by the mothers in spite of the very frequent visits and in spite of the fact that no treatment or medical advice was offered No refusals occurred A moderate drop out rate was mainly caused by households that moved from the area and by the temporary absence of some children Complete records were thus obtained for 216 children from 76 of the original households These 216 children constitute the study group dealt with in this chapter Information about the children s ages household income maternal education and age was obtained and classified as described elsewhere (м) In the middle of the study period children aged 12 59 months were weighed and weight for age calculated in per cent of the Harvard Standard (70)

4 2 MEDICAL CONCEPTS AND DEFINITIONS

As the data collected in this study were based on mother s reports and medical interference was avoided the identification of illness episodes had to be made when going through the protocols As recognized in other community based morbidity studies two main problems are encountered in this situation that of delineating new episodes and that of identifying different categories of illness Monto et al (100) recorded respiratory illness as new if at least two days without symptoms had elapsed between the end ot a reported illness and the development of another Also if there was a change in symptoms impressive enough to cause the respondent to call it a new illness it was classified as such A symptom-free interval of two days was also con-

sidered as the delineation between two illness episodes by Kamath et al (73) Acute upper respiratory infections were recorded as new by Buck (30) if more than 7 days had elapsed after the stated time of recovery from a previous infection Dingle et al (38) state that it is possible that a period of freedom from symptoms of infection does not necessarily mean that new symptoms appearing after a few days are the results of a new infection and that similarly it is quite possible to have a new illness superimposed on the remnants of a preceding one The use of clinical judgement is the only solution to this dilemma of defining illness when two or more symptoms are present at the same time Dingle et al had some evidence that many instances of respiratory and gastrointestinal symptoms occurring together represented the same infection but in some cases also two simultaneous diseases A similar approach was used by Fox et al in a surveillance study of viral diseases (47) Other reports reviewed in Chapter 1 are less explicit in their definitions of illness episodes

Definitions used in this study Periods of total illness regardless of the types of symptoms were considered to be delineated by at least two days of freedom from symptoms Illness was also divided into three different main categories gastroenteritis (diarrhoea and/or vomiting) respiratory illness (cough and/or symptoms of infection from throat or nose) and "other illness" (this group included such entities as fever with no other symptoms measles ear infection eye infection skin infection abdominal pain etc) Clinical experience from Ethiopia indicates that it is not uncommon for a child to suffer from several illnesses at the same time (80 113) Pneumonia may for instance be superimposed on a child already suffering from gastroenteritis who may also at the same time have trachoma the background being malnutrition and unhygienic living conditions causing a high risk and susceptibility f infections On the other hand it may be possible that for instance a virus infection may cause both respiratory and gastrointestinal symptoms (a classical example being measles which in this case was considered under other illnesses) For the sub-classification of illness it was therefore necessary to resort to judgement based on clinical experience when grouping simultaneously occurring symptoms into one or more illness episodes which were allowed to overlap Within each sub-group the elaps of at least two symptom-free days was considered to delineate episodes An analogous method of sub-division was also used within the heterogeneous group of 'other illness

This study contains the following three main samples of illness episodes

for further analysis total illness 427 gastroenteritis 147 respiratory illness 230 and "other illness 179 episodes It should be observed that according to the definitions used total illness episodes could be made up of consecutive or overlapping sub-groups of illness The sum of gastro enteritis respiratory illness and 'other illness' episodes therefore ex ceeds the number of total illness episodes In the following sections mathematical models suited to describe the distribution of illness incidence and duration will be tested on the empirical results from different age groups and sub-classifications of illness

4 3 FREQUENCY OF ILLNESS EPISODES OBSERVED AND FITTED DISTRIBUTIONS

The observed relative frequencies of illness episodes of different categories are illustrated in Figure 8 and Table A3 for the whole group of 216 children as well as for different age groups in comparison with the corre sponding probabilities $P(N=m)$ calculated under the model assumptions of a single Poisson distribution with parameter γ_H $(\hat{\gamma}_H = m)$ and a compound Poisson distribution with parameters α and β $(\alpha = m^2/(s_H^2 \quad m)$ $\beta \quad \bar{m}/(s_H^2 \quad m))$

As can be seen both in Figure 8 and in Table A3 and as measured by the χ^2 statistic the compound model fits the data remarkably well both for the total group and for the separate age groups The single Poisson distribution on the other hand produces a very poor fit for the whole group of children but gives a satisfactory description of the distribution of N for smaller and presumably more homogeneous age groups

It should be noted however that these distributions and the mean values of episode frequency given in Table 1 do not in a strict sense represent illness incidence as they include not only episodes that started within but also those that may have started before and were observed to terminate within the 60 day observation period When only episodes starting within the observation period are considered we get the incidence figures as given within brackets in Table 1 In fact the existence of truncated episodes both at the beginning and at the end of the observation period presents the problem of adjusting the observed distribution of episode duration A procedure for this purpose will be presented in Section 4 4

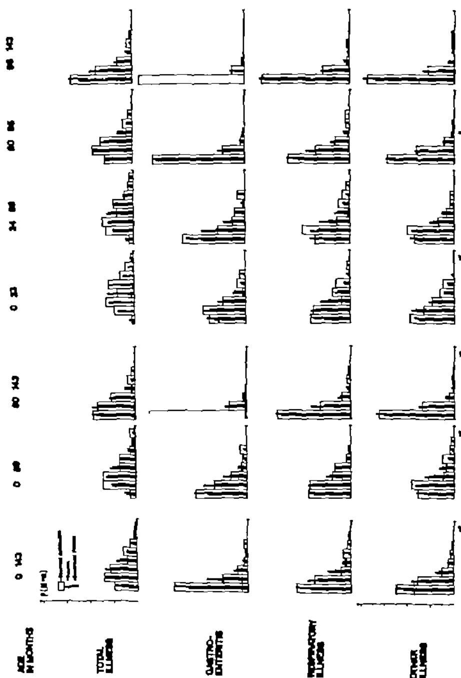


FIGURE 8 Obs rved frequency di tribution f numb f illness episode (M) observed d ring 60 day f obs rv tion by age and sub las ification of morbidity compared with the probability distributions calculated unde the assumptions f a ingle and compound Poisson mod l In case f inadmis ibl paramete stimates (when $m _ s_M^2$) the corresponding fitted di tribution has been omitted (Source Tabl A3)

TABLE 1 Mean number of illness episodes ($\bar{m}$) observed during a 60 day period in different age groups Figures within brackets denote mean number of episodes starting within the observation period

	Age (months)				
Sub-groups	0-23	24-59	60-95	96 143	0-143
Total illness	3 32 (2 76)	2 54 (2 82)	1 52 (1 10)	0 82 (0 61)	1 98 (1 63)
Gastro-enteritis	1 33 (1 19)	1 00 (0 86)	0 30 (0 27)	0 14 (0 10)	0 68 (0 59)
Respiratory illness	1 56 (1 31)	1 52 (1 25)	0 87 (0 58)	0 35 (0 29)	1 07 (0 86)
Other illness	1 19 (1 12)	1 14 (0 89)	0 60 (0 47)	0 41 (0 29)	0 83 (0 68)
	42	65	60	49	216

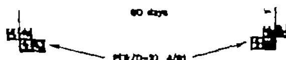
From the medical point of view the findings conform to the pattern observed in most morbidity studies Disease rates are highest in young children and then gradually decrease with age As can be seen in Tables A3 and 1 as well as in *Figure 8 this is especially obvious in diarrhoeal disease but less* pronounced in respiratory and other illness This pattern is often pointed out in studies from developing countries and is generally ascribed to the increased risk for gastrointestinal infections by contaminated foods during the weaning period and when the small child starts to crawl or walk around *in an unsanitary environment*

4 4 DURATION OF ILLNESS EPISODES ADJUSTING OBSERVED DISTRIBUTIONS FOR TRUNCATED EPISODES A MEASUREMENT PROBLEM

Since the present study was organized as a daily home visit study of predetermined length L = 60 days truncated episodes would occur at the beginning as well as at the end of the observation period As the actual duration of these episodes can not be assessed the statistical problem can be identified as how to use the selective information about the point of truncation to adjust the observed frequency distribution Omitting all truncated episodes would of course underestimate any group mean as within a randomly chosen interval of fixed length episodes of longer duration are more likely to occur

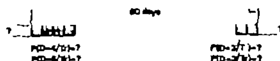
Initially we will regard D as a discrete variable with probability dis

tribution $P(D=t)$ i e episode lengths are assumed to be integers Furthermore it will be assumed that $P(D _ 59)$ 1



The probability as illustrated above that an episode of duration D 2 will be truncated at any end of the observation period $P(Tr|D=2)$ will be 4/61 0656 since out of 61 possible positions 4 will occur at an end point In half of these cases the observed duration t_0 equals the actual duration i e $P(Tr\ t_0\ 2|D=2)$ $P(Tr\ t_0\ 1|D=2)$ 2/61 Generally

$$P(Tr|D=t) \begin{cases} t & P(Tr\ t_0\ x|D\ t) = ?t/[L\ (t\ 1)] \quad t\ 1 \quad L\ 2 \\ & \qquad\qquad x=1 \qquad\qquad\quad t \\ 1 & \qquad\qquad\qquad\qquad\qquad\quad t\ L\ 1\ \ L \end{cases} \qquad (4\ 4\ 1)$$



Given that an episode has occurred at an end point as illustrated above what probability statement can be made about its duration? Since t_0 is the point of truncation we obviously have $P(D \geq t_0)$ 1 and consequently $\{t\ \ t _ t_0\}$ should be used as sample space when calculating $P(D=t|Tr\ t_0=x)$

Table 2 gives the unadjusted observed distribution (col 2 3) of n_E 56 gastroenteritis episode durations among n_c 42 children aged 0-2 years where f_{t_0} and f_t denote frequencies of truncated and nontruncated episodes respectively and where col 4 has been calculated from (4 4 1)

From Bayes theorem ($\bullet$ π) it follows that

$$P(D=t|Tr \quad t_0 = x) = \frac{P(Tr \quad t_0 \quad x|D=t) \quad P^{est}(D=t)}{\sum_{s \geq x} P(Tr \quad t_0 = x|D=s) \quad P^{est}(D=s)} \qquad (4\ 4\ 2)$$

where $P(D=t)$ has been denoted $P^{est}(D=t)$ serving as a first approxima tion in the iterative procedure and to be estimated from auxiliary sources or as in the present study be calculated from a random sub-sample within the physical observation period To ensure randomness only those episodes starting on days 2 30 were considered in the calculation of $P^{est}(D=t)$ (Col 5 in Table 2) The observations were grouped into classes 1 2 3 4 5 6-7 8 9 10-14 15-19 0-29 and 30-59 within which uniform distri butions were assumed

TABLE 2 The procedure f adjusting th distrib tion f illness dur ti ns of t uncated episodes llustr t- ed f a ample of 56 gastroent riti pisod s among children aged 0-2 y (F notations s text)

(1)	(2) f	(3) f_{t_T}	(4) (T |D=t)	(5) P^{est} (D=t)	(6) P(D=t|T t_0 x)	(7) P^{adj}(D=t)
1	3	2	0333	0357	[illegible]	05[illegible]
2	7	4	0656	1429	1590 1657 1544	1425
3	5	1	0968	1429	1638 [illegible] [illegible]	1118
4	3	2	278	0714	0801 0561 1 54	06[illegible]
5	6	0	1563	0714		1214
6	3	0	1246	0625		0658
7	5	0	2 21	0625		1014
8	0	0	2388	0625		0119
9	4	0	2647	0625		0831
10-11	2	1	3021	0428		0467
12-14	1	2	3649	0642		0420
15-19	0	0	4471	[illegible]		[illegible]
20-29	3	0	5063	1070		0544
30-39	0	0	7377	0238		0081
40-49	1	0	8957	0238		0073
50-59	1	0	2642	0238		0424
Σ	44	12		9997		1 0000

Application of (4 4 2) gives col (6) in Table 2 Thus the probability is 1590 that given that an episode truncated at t_0 1 has been observed it will be a two-day episode while it is 1657 if the point of truncation

is t_0 2 Accordingly

P^{adj} (D=2) 7/56 (2 0 1590 4 0 1657)/56 = 0 1425

Generally the probability that an observed episode will last t days is

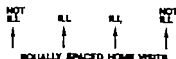
$$P^{adj}(D=t) = P(D=t \quad \overline{Tr}) + \sum_{x=1}^{t} P(D=t \quad Tr \quad t_0 \quad x) =$$

$$P(D=t \quad \overline{Tr}) \quad \sum_{x=1}^{t} P(D=t|Tr \quad t_0 = x) \quad P(Tr \quad t_0 \quad x)$$

which is estimated by

$$\frac{1}{n_B} [f_t \quad \sum_{x=1}^{t} P(D=t|Tr \quad t_0 \quad x) \quad f_{t_0}] \qquad (4\ 4\ 3)$$

We have hitherto regarded D as a discrete variable though D t are actually class midpoints with associated probabilities $P^{adj}(D=t)$ In order to be able to make probability statements like $P(D \le t)$ we should however take into account that these classes are not disjoint



As illustrated above D=2 as observed should actually be read {t 1 _ t 3} overlapping {t 0 t 2} the interpretation of D=1 Assuming that within each class with midpoint t_m

$P(D \quad t_m) \quad P(D _ t_m) \quad 1/2$

we get

$P(t _ D \quad t\ 1) \quad 1/2\ [P^{adj}(D=t) \quad P^{adj}(D=t\ 1)]$

and

$$P(D _ t) \quad \sum_{s=1}^{t\ 1} P^{adj}(D=s) \quad 1/2\ P^{adj}(D=t) \qquad (4\ 4\ 4)$$

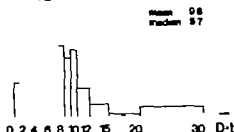


FIGURE 9 Adjusted obs rved dis t ibution of episode durati n in gastroente iti (ag g oup 0–23 months) (Sour : Table A4)

Applying (4 4 4) on data in Table 2 thus gives a continuous interpretation of the duration of *gastroenteritis* illness episodes *among* the youngest chil dren as displayed graphically in Figure 9

4 5 ADJUSTED DISTRIBUTIONS OF EPISODE DURATION medical interpretations

The adjusted distributions of episode duration for different categories of illness and age groups are illustrated by the histograms in Figure 10 and in cumulative form in Figure 11 (for illness duration up to 20 days) Means and medians are calculated from the corresponding numerical values given in Tables A3 and A4

It is immediately obvious that illness duration varies widely in all categories Furthermore the distributions are highly skewed mean values con sistently exceeding the median values due to a minority of episodes with long duration In general episode duration decreases with age which is especially obvious in the case of gastroenteritis whereas age differences are not so pronounced in respiratory illness Another striking feature is that some distributions have a bimodal shape which in the cumulative dis tributions is marked by a deviation from the smooth progression of the curves

From the medical point of view one may hypothesize about possible reasons for the above mentioned peculiarities As the acute illnesses dealt with in

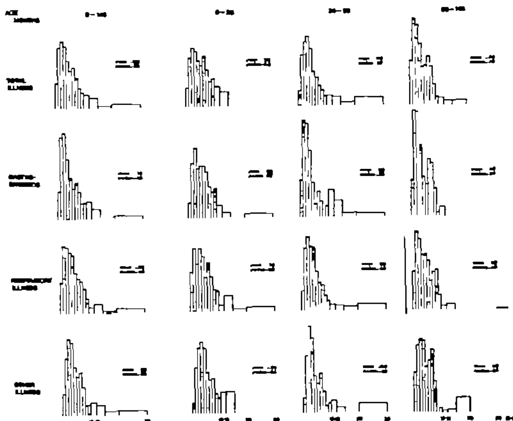


FIGURE 10 Adjusted ob rved di t ib tion f pisode dur tion i day (t) by illnes cat gory and ag (Source Tabl A4)

this study are mainly caused by infections the duration patterns may reflect both virulence factors in the causing agents and host factors involved in the body s defence against infections Older children may for instance have developed complete or partial immunity against highly contagious and naturally long-lasting infections (e g whooping chough) These infections would then be more common in the younger age groups Another possibility is that the longer illness duration would be a reflection of the young child s lower immunocompetence There is also increasing evidence that malnutrition has a detrimental effect on the immune functions especially those of the cell mediated immune system. The clinical effect of this is well known from for example the association between malnutrition and severe measles This association also prolongs the duration of measles episodes (44 48) Although this does not seem to have been systematically studied for a wider range of infections the high prevalence of malnutri

tion (Table 4) among the young children in this study may be a plausible explanation for the longer duration of their illnesses

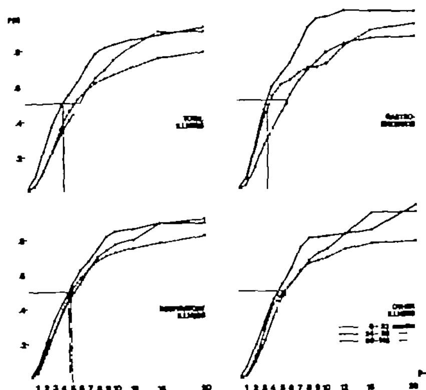


FIGURE 11 Adjusted bserv d cumul tiv di tribution of pi od du tion (in days) by illness at gory and ga (So rc Table A4)

The three main categories of illness dealt with here are naturally very heterogeneous The unspecific group of 'other illness' contains several different entities (4 2) but this is almost certainly also true of gastroenteritis and respiratory illness In a clinical study of children with diar rhoea (4e) Shigella enteropathogenic Escherischia coli Entamoeba histolytica Giardia lamblia and Strongyloides stercoralis were commonly observed pathogens As virological tests were not performed enteroviruses would probably be responsible for some of the cases with unidentified etiology and probably also enterotoxin producing Escherischia coli recently shown to be common among children in Addis Ababa (4a) Among these infections the parasitic ones would probably be of longer duration than the more acute bacterial and viral infections Also with regard to respiratory infections there is very little data about their viral etiology but there is reason to believe that this is both common and varied Clinical experience indi

cates the common occurrence of bacterial infections such as streptococcal tonsillitis pneumococcal pneumonia and tuberculosis It may be speculated that this etiological heterogeneity would be the most immediate explanation for the bimodal shapes of the distribution curves of illness duration and that host factors might determine some of the age differences The identifi cation of the microbiological spectrum of infections and of the patterns of immunocompetence in children needed to elucidate these problems is how- ever outside the scope of this study

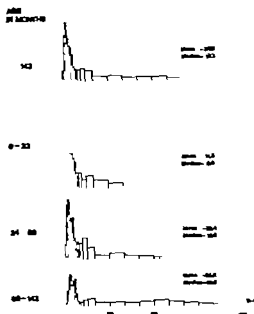


FIGURE 12 Adjusted observed di tribution f int rval dur tion (in day) between episodes of total illnes (Sou ce Tabl A5)

In analogy with an index of morbidity (in terms of time ill) it is possible to form a 'measure of health' in terms of time free from illness The peri ods of freedom from acute illness can also be studied with regard to their frequency and duration Figure 12 shows the distribution of duration of intervals between illness episodes In principle the calculations are based on the same adjustment procedure as described in 4 4 However in the calculations based on expression (4 4 2) $p^{est}(D=t)$ would have to be cal culated in a different way than for illness duration since the distribution of 'periods of health" is bound to present considerably larger variations and consequently we would get only limited information about the shape of

the distribution beyond for instance t = 30 days Therefore an exponential regression of the form F(t) 1-exp(a vt) was fitted to cumulative data in the range t < 30 and by means of which $p^{est}(D=t)$ for $t \geq 30$ could be extrapolated The results in Figure 12 confirm the pattern conconveyed by Figure 10 and Figure 11 The higher rate of illness episodes and their longer duration in young children than in older ones are thus also reflected by shorter intervals between the episodes

4 6 DURATION MODELS FITTED TO EMPIRICAL DATA

From the statistical point of view a more detailed analysis of variations in illness duration can be based on comparisons between the mathematical models and the empirical distributions Figure 13 thus displays in a cumu lative form the results of single exponential fits of illness duration in different age categories of the 216 children for a total of 427 total morbidity' episodes as defined in 4 2 corresponding to 556 partly over lapping episodes of gastroenteritis respiratory illness and other ill ness

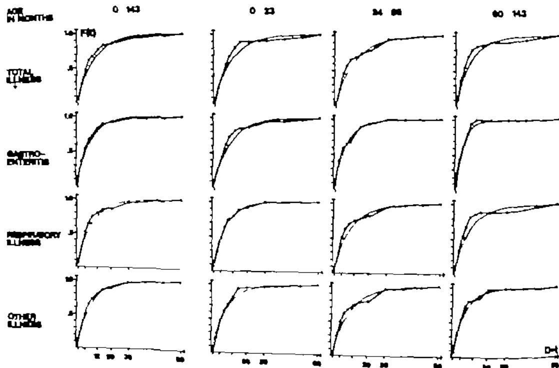


FIGURE 13 Adjust d cumul tive di t ibutions f epi ode dur tion ompar d with ingl xpone ti l fit (Source: Tabl A4)

Several of the observed distributions deviate somewhat from the fitted ex ponential by being more positively skew or by having a bimodal progression This may reflect sampling fluctuations or that the heterogeneity of the material is not well accounted for by the model

If we again consider as an example the distribution of the duration of gastroenteritis episodes in the age group 0-23 months a plausible assumption would be that there are significant age variations in episode duration within this age group especially as the process of weaning and the child s increased mobility may result in changes in the nutritional status and in the rate as well as the type of infection

In the Kirkos survey data were obtained indicating that almost all children under the age of 6 months were breast fed although this was often done in combination with bottle feeding and that at the age of 12 months 50 % of the children had been completely weaned This motivated a separate analysis of children below and above the age of one year showing a considerable dif ference between the two age groups (Figure 14) Episodes lasting 20-30 days are thus almost exclusively found in the lder age group

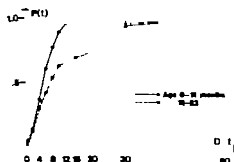


FIGURE 14 Adjusted observed cumulative dis ibution f dur tion f gast oenteri- ti p sode in g group 0-11 months (mean 7 2 and median 5 1 day) and 12 23 months (mean = 12 7 and median = 7 2 day) (Source Tabl A6)

We may also include all age groups 0-1 1 2 2 5 and 5-12 years in a four term mixed exponential distribution describing the distribution of gastro-

enteric illness duration

$$f(t) = \sum_{i=1}^{4} \pi_i \gamma_i \exp\{-\gamma_i t\}$$

where π_i is the relative number of episodes occurring in age group i and γ_i the corresponding parameter From Tables A6 and A7 we then get

$$F(t) \quad 31/147[1-\exp\{-0\ 1381\ t\}] + 25/147[1-\exp\{-0\ 0785\ t\}] +$$

$$65/147[1-\exp\{-0\ 1449\ t\}] \quad 26/147[1-\exp\{-0\ 2303\ t\}]$$

Figure 15 shows that a better fit is obtained when a mixed distribution (b) composed of four single exponentials (d) is used compared to one single exponential (a) fitted to the whole material of 147 episodes

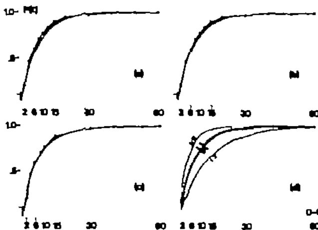


FIGURE 15 Adjusted cumulative distributions t gast oenteritis pisode dur tion (days) i g group 0-143 month compared with a ingl exponenti l fit (a) mixed exponential fit (b), an un tri ted xponential fit ( ) and exponential fit f f ur sepa t ag groups (d) (Source Table A7)

Reversely the mixed exponential could be used to identify sub-groups for a posteriori interpretation by letting duration of illness serve as a criterion for discrimination

This latter approach imposes an estimation problem Maximum-likelihood estimates exist in principle although not easily derived in the mixed exponen-

tial case ([illegible]) The method of moments ([illegible]) is convenient in the present case although it may produce inefficient and even imaginary estimates ([illegible]) when the two sub-groups are not too well separated i e when γ_1 is close to γ_2 A third method the method of quantiles simply equates percentage points and is a suitable method when data are censored at any tail of the distribution ([illegible]) but does not necessarily yield a unique or admissible set of estimates ([illegible])

The 147 gastroenteric episodes and their durations were also used to illustrate this unrestricted approach of identifying sub-groups The method of moments was used to estimate π γ_1 and γ_2 in a two-term mixed exponential Both from Figure 15 and from the numerical values (Table A7) we gather that both the age-mixed and unrestricted mixed exponentials are superior to the single exponential fit in accounting for the positive skewness of the distribution The age-mixed and unrestricted mixed distributions provide similar goodness of fits though they split the material in entirely different ways The unrestricted split may well be fictitious though the possibility cannot be precluded that it reflects other logical stratifications than that along the age dimension A well motivated clinical hypothesis would be that it reflects the respective etiology of two types of gastroenteric infections actually developing with different intensities or apart from age differences different groups of children with varying propensities to recover from a diarrhoeal episode

A special investigation into the distribution of episode durations of other infections was also undertaken Since this group all in all 179 episodes does not show any pronounced age differences as in the case of gastroenteritis and respiratory illness it may be justified to explore whether this group may reveal differences along other dimensions In the age group 5 12 years where the parameters of a two-term unrestricted mixed exponential could be estimated one could identify a smaller group with long durations (mean 16 8 days) as mainly composed of skin diseases while the remaining group with considerably shorter durations (mean 6 6 days) was dominated by eye disease ear infections and measles

On these grounds the 179 episodes were divided into three sub-groups skin diseases eye diseases and a group of other unspecified illness which also contained some cases of measles and eye disease Figure 16 based on the same type of adjustment process as described in 4 4 shows the distributions of episode duration in these sub-groups It is obvious that a group of epi



FIGURE 16 Adjusted obs rved dist ibutions f pisode duration (days) in three group of othe illness (Sour Tabl A8)

sodes of rather long duration are responsible for the high mean value in comparison with the median value It may also be added that it was possible to show that a three-term mixed exponential fit using these sub-groups provides a somewhat better fit than the single exponential

4 7 ASSESSING YEARLY INCIDENCE OF ILLNESS BACKGROUND VARIABLES

In Section 4 2 the results of the supplementary study were given in terms of the number of illness episodes *discovered* on 60 daily home-visits by category of illness and age A procedure accounting for truncated episodes was suggested in 4 4 by means of which an adjusted distribution of episode duration utilizing *all* episodes could be calculated

Within the frame of this study we may define a measure of illness load per year in the following two ways

number of illness *days* per year and child
number of illness *episodes* per year and child

Assuming a negligible seasonal variation the first approach would be equivalent to the calculation of

$$p = \bar{N} \ \bar{D}/L \qquad (4\ 7\ 1)$$

where $\bar{N}$ and $\bar{D}$ denote mean episode frequency per child and mean episode duration respectively calculated from L days of observation during which a fraction p of illness days were reported

A measure of yearly frequency of illness episodes will most conveniently be calculated by considering only episodes occurring, i e starting within the observation period If all episodes were to be utilized we have to take into account that truncated episodes extend beyond the physical observation period

Referring the subscript "Tr" to the group of children with truncated epi sodes and 'W' to the group of children with nontruncated episodes observed in full length *within* the observation period assuming that p_{Tr} is the same also after the physical observation period we have

$$\bar{L}_{Tr} \quad M_{Tr} \quad \bar{D}_{Tr}/p_{Tr} \qquad (4\ 7\ 2)$$

and

$$\hat{\mu}/\text{year} \quad 365[(n_{cW}\hat{\mu}_W/L_W) \quad (n_{cTr}\hat{\mu}_{Tr}/\bar{L}_{Tr})]/n_c \qquad (4\ 7\ 3)$$

Let the example introduced in 4 4 concerning n_p 56 gastroenteritis epi sodes with mean duration $\bar{D}$ 9 6096 among n_c 42 children again serve as an illustration Truncated episodes are observed for 11 of the 42 chil dren accounting for 28 of the 56 episodes Thus n_{cW} 31 n_{cTr} 11 $\hat{\mu}_W$ 28/31 0 9032 and $\hat{\mu}_{Tr}$ 28/11 2 5455 Mean episode duration in the two groups can be calculated as $\bar{D}_W$ 7 7143 and $\bar{D}_{Tr}$ 11 5049 218 illness days within the observation period are observed for the Tr-group of children Thus p_{Tr} 218/11 60 0 3303 and $\bar{L}_{Tr}$ 28 11 5049 60/218 88 66 Finally (4 7 3) gives $\hat{\mu}$/year 365[(31 0 9032/60) (11 2 5455/88 66)]/42 6 8 From Table 1 we get the corresponding number of episodes calculated from episodes occurring within the physical obser at on pe od as 1 19 365/60 7 2 The results of both procedures sum mari ed in Table A4 are similar This is one justification for the adjust ment procedure suggested in 4 4 If however frequency of illness occur rence is the ariable of interest we recommend that the simple procedure exclud ng left truncated episodes when counting number of episodes is uti lized

In Sections 3 and 4 3 mathematical models describing frequency of illness episodes were discussed. It was also shown that a single Poisson distribu tion would satisfactorily fit empirical data within each age group while a compound distribution was needed to account for different illness suscepti

bilities prevailing in an age heterogeneous material If this is also a valid assumption in the case of illness occurrence over a longer time e g one year $\hat{R}$/year would estimate the parameter γ_H in a Poisson model for a certain age and/or illness category Thus γ_H 6 8 would suffice to estimate $P(M=m) = \exp(\gamma_H)\ \gamma_H^m/m$ and the distribution of the number of gastroenteritis episodes among children aged 0 23 months could be stated hypothetically as in Figure 17

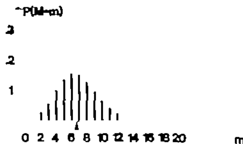


FIGURE 17 Hypothetical Poi son di tribution f the numb f gastroent riti pi ode pe year and child 0–23 month f ge

A comprehensive picture of morbidity as measured over a year can be based on a simultaneous interpretation of the hypothetical distributions of ill ness incidence in Figure 18 and the information about illness duration given in Table A4 The general pattern is most obvious in the case of gastroenteritis Thus children aged 0 23 months would suffer from 0 to around 19 episodes of diarrhoea per year (median 6 6) whereas children aged 5–12 years would have between 0 and around 7 episodes per year (median 1 0) The corresponding median duration would be 5 7 and 3 4 respectively Taking into account the measures of time ill given in Table A4 this means that there is a very marked difference in illness load due to diarrhoea between these two age groups Thus children in the younger age group can be calculated to suffer from diarrhoea on an average 63 days and the older children 4 days per year

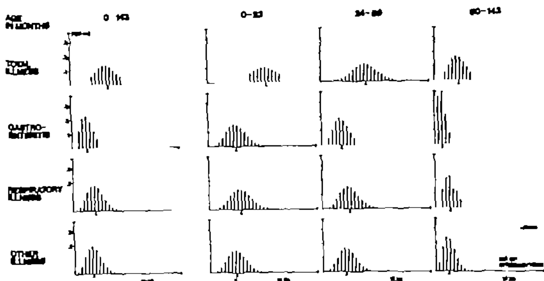


FIGURE 18 Hypothetical Poisson di trib tions f yea ly ill ness incidence by sub-classification f illness and g

Frequency and duration patterns of illness have so far only been analysed in relation to age This bivariate approach produces relevant results as the age factor is evidently a very trong determinant In a bivariate analysis of the morbidity patterns in relation to other factors however interactions between these factors and the age factor may have confounding effects This hould be borne in mind when interpreting the distributions of illness frequency and duration in relation to some other individual and household background factors for which information was available sex of the child nut tional status number of siblings household income maternal age and education As the results in the previous sections indicate that illness frequency varies more consistently with age than illness duration and as it is lso natural to assume that frequency rather than duration of illness would be influenced by socio-economic factors it was natural to start this analysis with study of illness frequency by sub-classes of the variables mentioned above (Table 3)

In children under 5 years girls had somewhat higher rates of observed illness than boys except with regard to gastroenteritis In the older age group differences between th sexes were small Information on weight for age was available for children aged 12 59 months and used as an expression of nutritional status Malnourished children (< 80 % of the Harvard Standard) had consistently higher morbidity values than the better nourished children

As infections are to some extent transferred between children in the same household (see 4 8) it could be expected that children in households with many children would on an average sustain more illness than those in households with few children This is however not reflected in a positive correlation between the number of episodes/child and the number of siblings probably due to a confounding effect from the age distribution

Low household income and maternal illiteracy were associated with high rates of illness in both age groups Maternal age below 30 years seemed related to high illness rates in the low age group of children

TABLE 3 Mean no f illne s epi od by ag and ther individual and household v iables
(n = numbe f children with compl t information
T t t l illnes G = gast oent iti R spi a tory illnes O the illn)

Variable	Class		Age 0-59 months					Age 60-143 months			
		n	T	G	R	O	n	T	G	R	O
Sex	Male	54	2.57	1.33	1.33	1.09	58	1.24	0.26	0.74	0.58
	Female	53	2.56	0.92	1.78	1.23	59	1.17	0.20	0.54	0.53
Weight for age % of standard *)	80	37	3.00	1.24	1.09	1.19					
	_80	46	2.33	0.93	1.46	1.09					
No. of siblings	0-1	43	3.07	1.65	1.47	1.44	21	1.95	0.24	0.71	1.14
	2-3	49	2.61	1.33	1.53	0.98	65	1.12	0.22	0.63	0.43
	4-5	15	2.40	0.73	1.60	1.07	23	0.74	0.26	0.57	0.17
Household income Eth. $ per month	100	40	3.17	1.35	1.79	1.21	37	1.73	0.41	1.11	0.57
	_100	48	2.46	0.90	1.40	1.13	59	1.02	0.14	0.44	0.54
Age of mother years	30	57	2.86	1.31	1.72	1.28	32	1.19	0.28	0.88	0.35
	_30	39	2.74	0.80	1.49	1.06	64	1.22	0.21	0.54	0.58
Education of mother	Illiterate	81	2.00	1.05	1.64	1.21	37	1.73	0.41	1.11	0.57
	Literate	22	2.41	1.41	1.14	1.14	7	0.57	0.14	0.29	0.14

*) Age group 12-59 months

Illness duration may be expected to correlate more directly with the individual variables than the household background variables Illness duration was therefore analysed according to the methods described in the previous sections in relation to sex and nutritional status Household income was chosen among the socio-economic variables for a similar analysis

The girls had somewhat higher adjusted values of the number of illness epi sodes (total illness) than the boys (Table 4) The boys on the other hand had higher proportion of time ill except in the age group 0 23 months This pattern was evidently caused by a concentration of illnesses with long epi sodes in boys aged 24 59 months The groups studied were however small and the variations may well be explained by chance

Illness incidence as measured by the estimated number of episodes per year showed the expected high values in the undernourished group for all illness categories (Table 4) No consistent pattern of association with episode duration was obvious but, higher proportion of time ill was consistently observed in malnourished children

Children in the low income households tended to have higher frequency and duration of illness than children in households with a higher income

TABLE 4 Adjusted measures of illness by sex nutritional status expressed as weight for age and household income (M= male F= female HS= Harvard Standard $\bar{N}$= mean number of illness episodes per year $\bar{D}$= mean episode duration $\tilde{D}$= median episode duration p= mean proportion of time observed ill)

Illness category	Age group (months)	Variable	Class		$\bar{N}$	$\bar{D}$	$\tilde{D}$	p
Total illness	0-23	Sex		23	3 7	8 7	5 5	0.32
			F	20	6.5	5	7 8	0 46
	24-59			32	9 8	15.6	1 6	0.41
				33	13.0	7 4	4 6	0.27
	60-143			50	5 7	8 2	4 7	0.14
				59	5 7	7 8	4 9	0.11
	0-143			104	8 8	11.2	4.6	0.26
				112	9 8	8 9	4 9	0.23
Total illness	12-59	Weight for age % of HS	<90	37	16.	8 5	5.7	0 43
			≥90	46	8 2	2.8	6 1	0.35
Gastro-enteritis			<90	37	6.7	8 7	5 6	0.16
			≥90	46	6 7	7.6	3.5	0.18
Respiratory illness			<90	37	8 5	8 5	6 9	0.22
			≥90	46	6.4	7 7	5 9	0.1
Total illness	0-59	Household income Ksh /month	<100	40	13 9	7 9	5.4	0. 1
			≥100	40	12.8	9 3	6 3	0.31
	60-143		<100	37	6 7	10 5	4 4	0.28
			≥100	58	4 7	9 4	5.2	0.11

The individual and household background variables discussed above may be even more important than revealed since they probably interact with each

other and the age factor A general conclusion would however be that individual variables – apart from the age variable and socio-economic variables do influence morbidity especially when measured in terms of incidence rates and total time ill A more extensive multivariate analysis also including several other socio-economic variables will be presented in Chapter 7

4 8 INTRODUCTION AND SPREAD OF ILLNESS WITHIN HOUSEHOLDS

Morbidity studies of the present type have formed various indices of illness introduction into households and illness spread within households and have used these to obtain information about the spread of infections in the community about contagiosity susceptibility and also about incubation times ([illegible]) This will also be attempted here even though the analysis will be somewhat limited due to the fact that only children were studied

After an examination of the records it is obvious that episodes of both gastroenteritis and respiratory illness tended to occur in small outbreaks within the households In order to quantify this impression the rate at which an illness episode in a household member was followed by illness in other household members was measured against the coincidental incidence of illness in the study group outside the household judged to reflect the random occurrence of illness during the same period Illness both in the household and outside the household starting on the same day as a certain individual illness episode or during the 10 days after is termed *secondary occurrence* The term is not intended to imply a causal relationship

The proportions of 'secondary occurrence' among the number of possible candidates for 'secondary occurrence" on each of the 10 days from the start of all single illness episodes in the material were weighed into general measures of secondary occurrence'

$$P(S_t) = \begin{cases} s_{wt} / \sum\sum\sum_{ijv} (n_{c_i} \; 1) & \text{"within households'} \\ \\ s_{ot} / \sum\sum_{ijv} (n_c - n_{c_i}) & \text{outside households} \end{cases} \qquad (4\ 8\ 1)$$

where

i	1	n_h	households
j	1	n_{c_i}	children in household no i (n_c $\Sigma_i n_{c_i}$)
v	1	$n_{E_{ij}}$	episodes for child no (i j)

and

s_{wt} and s_{ot} denote the sum of all observed secondary occurrences on day t after the start of an illness episode within and outside households respectively

TABLE 5 Results of analy is f secondary occurrenc f illnes within and outside households

Illness	n_h	n_c Number of possible secondary occurrences within	outside	No. of observed secondary occurrences within household on day no.	outside household on day no.
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

The results given in Table 5 and Figure 19 show that "secondary occurrence" within-household is considerably higher for both gastroenteritis and respi ratory illness than it is for secondary occurrence" outside-household which in its turn indicates the stable level of naturally occurring illness in the community The high within-household-rate on day 0 indicates that children in a household have a tendency to fall ill simultaneously this is rather natural as many of the episodes included in the measure are other than primary cases in a household outbreak It does not necessarily imply that multiple introductions are common The bimodal shape of the curves (Figure 19) especially in the case of gastroenteritis may possibly be caused by diff rences in incubation time There may be one group of epi sodes with a short incubation time (a few days) and one group with long incubation periods (6-7 8 days)

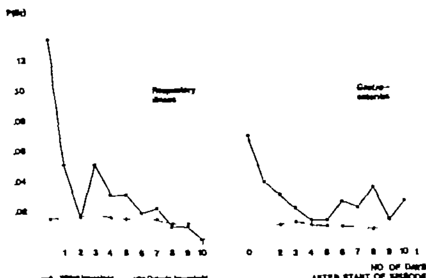


FIGURE 19 Patt rn of a ondary occurrence of acut illness (Source: Table 5)

Having verified the tendency to intra household spread of illness this may be analysed more in detail although the study was not originally designed for this purpose Household outbreaks the corresponding *index cases* (chil dren introducing illness into the households) and secondary cases were thus identified by the use of certain criteria in the examination of the records A household outbreak of gastroenteritis or respiratory illness thus started with an index case defined as a case appearing 10 or more days after the onset of the last individual episode of the respective illness in the house-hold For each of the other siblings the first illness during the nine day period following the onset of an index case was termed a secondary case These definitions are in accordance with the previous analysis of second ary occurrence' and with definitions used elsewhere (m) If two or more individual episodes appearing on the same day fulfilled the criteria for an index case they were considered to constitute a *multiple index case* or a *multiple introduction*

Because of these restrictions index cases were selected from a 41-day pe-riod of the 60-day study period (day 11 to 51) In order to obtain any mea sures of introduction into and spread of illness within households the fact that adults may introduce illness or be infected by children had to be dis regarded as information from adults was not obtained This was however thought to be justified as in other materials children have been shown to

be the main introducers of acute illness (so as so) and in view of the high rates of infection in the younger children in this material The following analysis should therefore be interpreted with great caution although the relevant information which it seems to provide may justify its inclusion

Introduction rate were calculated as the number of index cases per child and month (*Table 6*) *The expected number of index cases was calculated assuming* that they should be proportional to the number of children as well as to the overall frequency of illness (Table A4) in the respective age groups The ratio (*introduction ratio*) between the obse ved and expected number of cases give *an indication of the relative risk of introducing* illness in the various age groups This may be exemplified by the results (Table 6) for children aged 0 23 months who had an average introduction rate of gastroenteritis *of 0 42 per child and month This is 2 42 times the expected* value *assuming a rate* proportional to the size of the age group and 1 24 times the expected value if in addition the rate is assumed to be proportional to the overall gastroenteritis frequency in the age group Children over 5 years had an introduction rate of only 0 24 which is 0 23 and 0 67 of the respective expected values With the reservation that adult household members were not studied the general implications of the results are that preschool children introduce the bulk of both gastroenteritis and respiratory illness into the households and that this is done at a rate that exceeds the expected value especially in age group 0 3 months

TABLE 6 I troduction te and econdary ttack
t i gast oe t riti and re pi t ry illn

[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

[illegible]

The high introduction ratio of gastroenteritis in children under 2 years may be an effect of unhygienic food handling and that in older preschool children also of their intimate contact with unsanitary surroundings The high introduction ratios of respiratory illness may indicate that children in these age groups have a high degree of contact with other infected chil dren or adults

Household introduction rates are given in Table 6 These were also studied in relation to the number of children per household On an average the number of index cases rose with the increase in the number of children In households with 4-6 children it was however somewhat lower than could be expected probably due to a larger proportion of older children

The rate of multiple introductions was low two of 51 gastroenteritis and four of 44 respiratory index cases were multiple For gastroenteritis this may be taken as evidence against the epidemic spread of food or waterborn infection and favours contact spread as the main mode of transmission (*18,81*)

Secondary attack rate was calculated (Table 6) a. the number of secondary cases per exposed child For gastroenteritis the secondary attack rate was highest in children aged 0-23 months probably indicating a high suscepti bility to infection For respiratory illness the highest value was found in the age group 2 5 years The limited material did not allow the study of the secondary attack rate in different age groups according to the category of introducer

The interval between the onset of the index case and secondary illness was 1 3 days in seven and 6-9 days in eight of the secondary gastroenteritis cases This may possibly indicate that there are two groups of infections with different incubation times and could be interpreted in accordance with the results given in Table 5 and Figure 19 For secondary cases of respira tory illness the mean interval was 3 7 with a range of 1 7 days

4 9 SOME MEDICAL PERSPECTIVES

The main purpose of this supplementary study of illness frequency and dura tion was to obtain an empirical basis for certain assumptions about the statistical properties of their respective distributions needed for the evaluation of the measure of illness load employed in the one-year morbidi

ty study Medical literature provided only very limited documentation in this respect The analysis of frequency and duration of illness also included the problem of dealing with truncated episodes observed at the beginning and at the end of the observation period and for which the duration was not known An estimation procedure was suggested and applied in the calculation of adjusted distributions of illness duration and adjusted values for the observation period This also made it possible to use the data on truncated episodes in the formation of measures of illness incidence

The data obtained in this study also provide the basis for some epidemiologic measures of illness introduction into and spread within the households with some reservations about their validity as adult household members were not studied According to the introduction rates (0 42/child/month) children under the age of two years seemed to be the main introducers in family outbreaks of diarrhoeal disease Similar conclusions were reached in a study from rural Guatemala (*) In comparison with figures from Guatemala (* *) the children in our study exposed to diarrhoeal disease had a higher average secondary attack rate (15 %) The highest values were found in children under the age of two years which may be taken as evidence for their high susceptibility This pattern was also noted in the Guatemalan studies For respiratory illness the average introduction rate of 0 15 per child and month was similar to what has been reported from studies carried out in the USA and England (* * *) which in general found the highest values in school children whereas in this study the youngest age group had the highest rates The average secondary attack rate was 19 % and the highest values (31 %) were found in children aged 2 4 years American studies reported secondary attack rates in infants and preschool children of 30-50 % (*)

The results with regard to observed levels and distributions of illness frequency and duration confirmed the general pattern of childhood morbidity reported in community studies from other developing countries as reviewed in Table 7 Thus a high average incidence of gastroenteritis in children under 2 years (in our material 6 8 episodes/year) was also reported from India Indonesia Costa Rica Egypt and Ethiopia Some studies from rural villages in Guatemala however showed lower incidences similar to those observed in the USA and in England (* *) whereas their values on the duration of diarrhoeal episodes correspond to our findings of a mean duration of 9 6 days (median 5 7) in the youngest age group Older children had considerably lower rates of diarrhoea of shorter duration These age dif

ferences are especially obvious if illness load is calculated in terms of total time observed ill Children under the age of two years could thus be estimated to suffer from diarrhoea on an average 63 days per year whereas the corresponding figure for children over the age of 5 years was 4 days which is in conformity with the findings of another Guatemalan study (●)

Similar age differences were observed for respiratory illness although less pronounced than for gastroenteritis Children under 2 years were estimated to have an average of 7 9 attacks per year while 6 6 and 3 2 attacks per year were estimated for children aged 2 5 and 5 and above respectively (Table A4) As can be seen from Table 7 these figures correspond to what has been reported from other developing countries (except for some studies from Guatemala) and differ very little from what has been observed in the USA

Variations in different measures of morbidity especially illness duration were less pronounced when studied in relation to household background vari ables and to individual variables other than age However bivariate analyses indicated moderate but consistent associations between low nutritional status low household income maternal illiteracy and high values of ill ness incidence and time observed ill The latter measure used by us as an indicator of illness load will be evaluated in the following chapter

TABLE 7 F equency and duration of illnes pis de A review f some community based longitudinal mo bidity tudi see next page (N f illne episodes ar given per year which mean th t e- calculations hav been pe f rmed in eve al instance Illness dur tion i given in day)

TABLE 7

CHAPTER 5

MEASURING MORBIDITY BY MEANS OF EQUALLY SPACED OBSERVATIONS —
Evaluation of measure and design in the one-year study

5 1 TOOLS FOR EVALUATION THE MODEL OF ILLNESS OCCURRENCE

In this chapter we will proceed under the assumption of a two-state alter nating Poisson process for which the justifications have been discussed in Chapter 4 With our present knowledge of the problem we consider this a fairly realistic model a hypothesis that empirical data have so far not rejected This model will now serve as our tool in evaluating the illness load measure generated from the one-year home-visit study It should be noted then that $\mu_{jD}/(\mu_{jD}+\mu_{jH})$ stands for the true individual morbidity (P_j) and where $\gamma_{jD} = 1/\mu_{jD}$ and $\gamma_{jH} = 1/\mu_{jH}$ are parameters in the two exponentials describing the individual child s duration of illness (*"recovery propens ty)* and health episodes (*"illness susceptibility)* respectively It is obvious that the two-month daily home-visit study could not collect enough episodes for each individual child Since there is support from data that the more homogeneous the group is the better the models fit data especially with regard to age we will assume that γ_D i e the reciprocal of mean episode duration can be estimated from all episodes gathered within the age groups while γ_{jH} the reciprocal of mean duration of 'health episodes will have to be specified for each child This means that we permit each child to have its own illness susceptibility while children belonging to the same age groups are considered to have the same recovery propensity

Now let us consider the process at two time points t and t τ By virtue of the Markov property (**) (i e that the probability of future behaviour of the process when its present state is known is not altered by additional knowledge of its past behaviour) the probability that the child is ill at both time points is

$$P[x(t\ \tau)\quad x(t)\quad 1]\quad P[x(t+\tau)\quad 1|x(t) = 1]\quad P[x(t)\quad 1]$$

$$= P[x(\ )\quad 1|x(0)\quad 1]\quad \gamma_{jH}(\gamma_D+\gamma_{jH})$$

Further it can be shown that

$$P[x(t+\tau)=1|x(t)=1] = \gamma_{jH}/(\gamma_D+\gamma_{jH}) + [\gamma_D/(\gamma_D+\gamma_{jH})]\exp[-\tau(\gamma_D+\gamma_{jH})] \quad (5\ 1\ 1)$$

and

$$P[x(t+\tau)=x(t)=1] = \gamma_{jH}^2/(\gamma_D+\gamma_{jH})^2 + [\gamma_D\gamma_{jH}/(\gamma_D+\gamma_{jH})^2]\exp[-\tau(\gamma_D+\gamma_{jH})] \quad (5\ 1\ 2)$$

which are functions of time only through the "spacing" τ Empirical illustrations of (5 1 1) and (5 1 2) are given in Figure 20 Mean duration of total illness in age groups 0–23 24 59 and 60–143 months (Table A4) have been used to represent three individuals with parameters $(\gamma_D\ \gamma_{jH})$ (0988, 0324) (0896 0149) and (1186 0063) which correspond to P_j-values 0 2469 0 1427 and 0 0505 respectively The observed mean values have been calculated from the *one-year study* for those children who were followed by home-visits for most of the year (■)

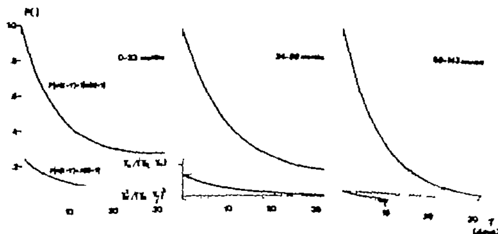


FIGURE 20 Th probability f illne on two occa ions [illegible] between oc asions unde the as umptions f an lternating [illegible] $(\gamma_D\ \gamma_{jH})$ (0988 0324) (0896 0149) and (1186 [illegible]

Since (5 1 1) expresses the conditional probability that [illegible] a certain day given that he was ill days earlier [illegible] d t onal probab lity of him being ill on two occasi[illegible] respective curves ill tart (τ 0) at 1 and P_j [illegible] true indiv dual morbidity

Also the rate of decrease towards

$$\lim_{\tau\to\infty} P[x(t\ \ \tau) = 1|x(t)\quad 1]\quad \gamma_{jH}/(\gamma_D\quad \gamma_{jH})$$

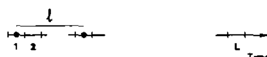
and

$$\lim_{\tau\to\infty} P[x(t\ \ \tau) = x(t)\quad 1] = \gamma_{jH}^{2}/(\gamma_D\quad \gamma_{jH})^{2}$$

respectively reflect the successive departure from dependent observations

5 2 SOURCES OF VARIATION IN STUDY DESIGN

In general terms each child was observed on v occasions with equal intervals ℓ during a period of L v ℓ days as illustrated below



At the time of each fortnightly home-visit children were recorded as "ill or 'not ill with regard to total illness and sub-classifications of illness as described in 2 3 Thus for each child morbidity as expressed by the proportion of the total number of visits on which the child was recorded as ill represented the total load of illness during the observation period

In statistical terms the measurement procedure could be expressed as follows

the estimation of *individual morbidity* by means of the measure

$$p_j \quad \sum_{i\ 1}^{v} x_{ij}/v$$

where

$$x_{ij} \quad \begin{cases} 1 & \text{if child no } j \text{ is observed ill on home visit no } i \\ 0 & \text{if child no } j \text{ is not observed ill on home visit no } i \end{cases}$$

the estimation of *group morbidity* using

$$p \quad \sum_{j\,1}^{n_c} p_j/n_c$$

where n_c number of children

When using longitudinal series of observations in this study two main problems were encountered

the assessment of the validity and the statistical precision of the measures

the handling of incomplete series of observations due to drop-outs and non response

In order to assess the statistical properties of the measures the following has to be taken into account

For the individual measure the variation is partly due to the individual s illness pattern and partly to the sampling error introduced by the systematic sampling of interview occasions Also the precision is a function of the intensity in home visiting i e of t and of the length (L) of the observation period

For the group measure an additional sampling error is introduced caused by the sampling of children (Figure 21)

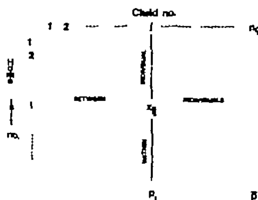


FIGURE 21 Sources f variation in the longitudinal home vi it design.

5 3 CRITERIA FOR EVALUATION

5 3 1 *The individual measure*

When evaluating the properties of the measure $p_j = \sum_{i=1}^{v} x_{ij}/v$ we may consider the observations at equally spaced time points as measuring in discrete time the underlying continuous process described in Chapter 3

Further the indicator variable x_{ij} is Bernoulli distributed (41) with

$$E(x_{ij}) = P(x_{ij} = 1) = \gamma_{jH}/(\gamma_D+\gamma_{jH}) \quad P_j$$

the true morbidity for child number j Thus

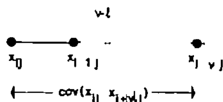
$$E(p_j) = \sum_i E(x_{ij})/v = P_j$$

and p_j is an unbiased estimator of P_j

If the longitudinal observations ℓ days apart could be regarded as in dependent we would get the simple binomial variance of p_j

$$P_j(1 \quad P_j)/v = \gamma_D\gamma_{jH}/v(\gamma_D+\gamma_{jH})^2 \qquad (5\ 3\ 1)$$

This may be justified when ℓ is large enough which in practice means that the child will get some time to recover between consecutive home-visits (see Figure 20) For general solutions however the covariance structure as illustrated below must be accounted for



From (5 1 2) the autocovariance function is

$$\mathrm{cov}(x_{ij} \ x_{i+v\ j}) \quad E(x_{ij}x_{i+v\ j}) \quad E(x_{ij}) \quad E(x_{i+v\ j}) \quad P[x_{ij} \quad x_{i+v\ j} \quad 1]$$

$$\gamma_{jH}^2/(\gamma_D+\gamma_{jH})^2 \quad [\gamma_D\gamma_{jH}/(\gamma_D \ \gamma_{jH})^2]\exp(\ v\ell(\gamma_D \ \gamma_{jH}))$$

This implies the following corresponding autocorrelation function

$$\rho(x_{ij}, x_{i+v\,j}) = \mathrm{cov}(x_{ij}, x_{i+v\,j})/V(x_{ij}) = \exp[-v\ell(\gamma_D+\gamma_{jH})] \qquad (5.3.2)$$

Figure 22 shows the value of ρ as a function of $v \cdot \ell$ for three hypothetical values of $\gamma_D+\gamma_{jH}$ (compare the values in Figure 21). We can gather for instance that in a *fortnightly home visit design the correlation between consecutive observations* ($v = 1$, $\ell = 14$) is approximately 0.25 while the corresponding value in a weekly home visit study would be around 0.50 ($v = 1$, $\ell = 7$). The correlations between every second home visit is 0.06 ($v = 2$, $\ell = 14$) and 0.25 ($v = 2$, $\ell = 7$) respectively. Furthermore under the model assumptions we gather that in a fortnightly design and for $\gamma_D+\gamma_{jH} \geq 0.10$ the autocorrelation may be neglected and thus $V(p_j)$ calculated under the assumption of independent observations.

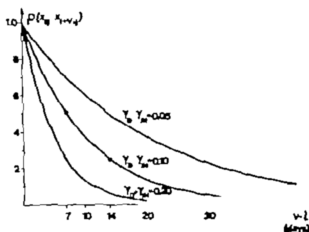


FIGURE 22 The autocorrelation between home-visit morbidity observations as a function of study design (ℓ = space between home visits; v = home visit number) and exponential model parameters ($1/\gamma_D$ = mean duration of illness episodes; $1/\gamma_{jH}$ = mean duration of the jth episodes)

The precision of p_j as measured by the variance function is

$$V(p_j) = V\Big(\sum_{i=1}^{v} x_{ij}/v\Big) = \frac{1}{v^2}\Big[\sum_i V(x_{ij}) + 2\sum_{\nu=1}^{v}(v-\nu)\mathrm{cov}(x_{ij}, x_{i+\nu\,j})\Big]$$

$$= \frac{1}{v}\big[\gamma_D\gamma_{jH}/(\gamma_D+\gamma_{jH})^2\big] + \frac{1}{v^2}\big[2\gamma_D\gamma_{jH}/(\gamma_D+\gamma_{jH})^2\big]\sum_{\nu=1}^{v}(v-\nu)\exp[-\nu\ell(\gamma_D+\gamma_{jH})]$$

$$= \frac{1}{v}\,[\gamma_D\gamma_{jH}/(\gamma_D+\gamma_{jH})^2][1+2\sum_{v=1}^{V}(1\ \frac{v}{V})\exp\{-v\cdot\ell(\gamma_D+\gamma_{jH})\}] \qquad (5\ 3\ 3)$$

Figure 23 illustrates the magnitude of the correction term (the last factor within brackets in (5 3 3) accounting for dependent longitudinal observations) and the corresponding variance as functions of both illness susceptibility (γ_{jH}) and recovery propensity (γ_D) when $v = 26$ and ℓ 14

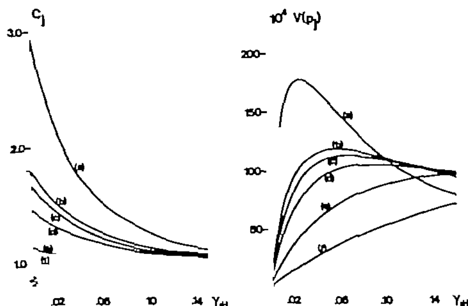


FIGURE 23 Th correction t rm (C_j) f dependent longitudinal observations (th f to by which the impl binomial varianc i multiplied) as a function f illnes uscaptibility γ_{jH} and re ov ry propensity γ_D illustrated fo f tnightly visits during one ye (v=26 ℓ=14) In ( ) (b) and (d) γ_D has been estimated from the di tribution f episod duration in age group 0-23 24-59 and 60-143 months espe tiv ly whil (a) (e) and (f) r present thr hypotheti al cases

	(a)	(b)	( )	(d)	(e)	(f)
γ_D =	0 05	0 0896	0 0988	0 1186	0 20	0 50

It can thus be seen that with increasing γ_D the correction term approaches 1 0 and consequently $V(p_j)$ will gradually coincide with that of the binomial variance expression (5 3 1) The departure from dependent observations is also reflected by an assymetry in $V(p_j)$ as regards the γ_{jH} axis By analogy as γ_{jH} increases less account has to be taken of the correction term on all practical levels of γ_D Reversely a two- or

threefold increase in variance as compared with the binomial case may be the result if illness occurs less frequently but with episodes of long duration It is thus essential that some knowledge of episode duration is gathered and considered when evaluating measures of illness load like the one used in this study

5 3 2 The group measure

The longitudinal home visit design involves two sources of variation one due to the systematic sampling of interview occasions the other caused by the sampling of children both of which have to be taken into account when assessing the statistical properties of

$$p \quad \sum_{j\;1}^{n_c} p_j/n_c \quad \sum_{i\;1}^{v} \sum_{j\;1}^{n_c} x_{ij}/vn_c \qquad (5\ 3\ 4)$$

the estimator of P the mean proportion of illness per child and time unit in the population

For a given child j p_j estimates P_j then considered a fixed parameter where $E(p_j/P_j) \quad P_j$

For a group f children however P_j is to be looked upon as a random variable with $E(P_j) = P$ and variance $\sigma_P^2 = V(P_j)$ Thus

$$E(p) = \sum_{j\;1}^{n_c} E(p_j)/n_c = \sum_{j\;1}^{n_c} E[E(p_j/P_j)]/n_c \quad \sum_{j\;1}^{n_c} E(P_j)/n_c \quad P \qquad (5\ 3\ 5)$$

For a random sample of children

$$V(p) \quad \sum_{j\;1}^{n_c} V(p_j)/n_c^2 \quad \sum_{j\;1}^{n_c} \{V[E(p_j/P_j)] \quad E[V(p_j/P_j)]\}/n_c^2 =$$

$$\sigma_P^2/n_c \quad \sum_{j\;1}^{n_c} E[C_j \gamma_D \gamma_{jH}/v(\gamma_D+\gamma_{jH})^2]/n_c^2 \qquad (5\ 3\ 6)$$

where

$$C_j \quad 1 \quad 2 \sum_{\nu=1}^{v} (1 \quad \frac{\nu}{v}) \exp(\nu\, \ell(\gamma_D \quad \gamma_{jH})) \qquad (5\ 3\ 7)$$

is the correction term for autocorrelation.

$$= \frac{1}{v}\,[\gamma_D\gamma_{jH}/(\gamma_D+\gamma_{jH})^2][1\ \ 2\sum_{v=1}^{V}(1\ \ \frac{v}{V})\exp(\ v\ \ell(\gamma_D+\gamma_{jH}))] \qquad (5\ 3\ 3)$$

Figure 23 illustrates the magnitude of the correction term (the last factor within brackets in (5 3 3) accounting for dependent longitudinal observa tions) and the corresponding variance as functions of both illness susceptibility (γ_{jH}) and recovery propensity (γ_D) when $v = 26$ and ℓ 14

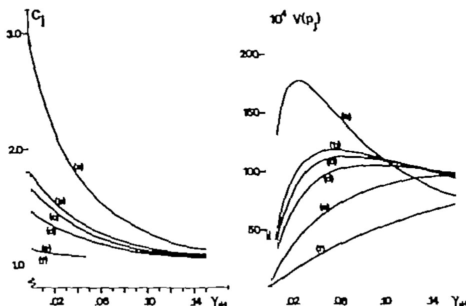


FIGURE 23 Th ection t rm (C_j) fo dependent l ngitudinal b servations (th fact r by which the impl binomial va iance i multiplied) as a function of illnes usc ptibility γ_{jH} nd re ov ry propensity γ_D illustrated f f rtnightly visits during ne year (v=26 ℓ=14) In ( ) (b) and (d) γ_D has be n stimated f om the distribution f pisod duration in ge group 0–23 24 59 and 60–143 months r pectively wh l (a) (e) and (f) ep esent three hypoth tical cases

	( )	(b)	( )	(d)	(e)	(f)
γ_D	0 05	0 0896	0 0988	0 1186	0 20	0 50

t can thus be seen that with increasing γ_D the correction term approaches 1 0 and consequently $V(p_j)$ will gradually coincide with that of the binomial variance expression (5 3 1) The departure from dependent observations is also reflected by an assymetry in $V(p_j)$ as regards the γ_{jH} axis By analogy as γ_{jH} increases less account has to be taken of the correction term on all practical levels of γ_D Reversely a two- or

threefold increase in variance as compared with the binomial case may be the result if illness occurs less frequently but with episodes of long duration. It is thus essential that some knowledge of episode duration is gathered and considered when evaluating measures of illness load like the one used in this study

5 3 2 The group measure

The longitudinal home visit design involves two sources of variation one due to the systematic sampling of interview occasions the other caused by the sampling of children both of which have to be taken into account when assessing the statistical properties of

$$p = \sum_{j\ 1}^{n_c} p_j/n_c \quad \sum_{i=1}^{v} \sum_{j\ 1}^{n_c} x_{ij}/vn_c \qquad (5\ 3\ 4)$$

the estimator of P the mean proportion of illness per child and time unit in the population

For a given child j p_j estimates P_j then considered a fixed parameter where $E(p_j/P_j) \quad P_j$

For a group of children however P_j is to be looked upon as a random variable with $E(P_j) \quad P$ and variance $\sigma_p^2 = V(P_j)$ Thus

$$E(p) \quad \sum_{j\ 1}^{n_c} E(p_j)/n_c = \sum_{j\ 1}^{n_c} E[E(p_j/P_j)]/n_c = \sum_{j\ 1}^{n_c} E(P_j)/n_c \quad P \qquad (5\ 3\ 5)$$

For a random sample of children

$$V(p) \quad \sum_{j\ 1}^{n_c} V(p_j)/n_c^2 \quad \sum_{j\ 1}^{n_c} \{V[E(p_j/P_j)] \quad E[V(p_j/P_j)]\}/n_c^2$$

$$\sigma_p^2/n_c \quad \sum_{j\ 1}^{n_c} E[C_j \gamma_D \gamma_{jH}/v(\gamma_D+\gamma_{jH})^2]/n_c^2 \qquad (5\ 3\ 6)$$

where

$$C_j \quad 1 \quad 2 \sum_{v=1}^{V} (1 \quad \frac{v}{V}) \exp(\quad t(\gamma_D \quad \gamma_{jH})) \qquad (5\ 3\ 7)$$

is the correction term for autocorrelation

Since exp{ } is a rapidly decreasing function especially for practical sizes of ℓ the following approximation may be justified

$$C_j = 1 + 2 \sum_{v=1}^{\infty} \exp\{ v\ell(\gamma_D + \gamma_{jH})\} =$$

$$= 1 + 2 \exp\{ \ell(\gamma_D + \gamma_{jH})\}/[1 \quad \exp\{ \ell(\gamma_D + \gamma_{jH})\}] =$$

$$[1 \quad \exp\{ \ell(\gamma_D + \gamma_{jH})\}]/[1 - \exp\{ \ell(\gamma_D \quad \gamma_{jH})\}] \qquad (5\ 3\ 8)$$

Though aware of the design effects (m) introduced when a cluster sample with households as primary and children as secondary units is treated as a simple random sample of children we will not attempt to make things more complex at the present stage It may be added however that the induced intra-household correlation coefficient i e a measure of homogeneity between children belonging to the same household with regard to illness experience is of the order 0 34 and that this would imply an increase in variance of about 1 6 times that calculated from (5 3 6) The consequences of design effects will be subject to further study and will be reported elsewhere (m)

It has also been assumed above that γ_D is constant between children within age homogeneous groups (0–23 24 59 and 60–143 months) i e having the same underlying mean duration of illness episodes while γ_{jH} and consequently P_j are subject to variation

V(p) as decomposed in (5 3 6) contains two variance components to be estimated from data

The variation "between children"

$V_B \quad \sigma_p^2 / n_c$ is easily estimated by

$$V_B \quad \sum_{j\ 1}^{n_c} (p_j \quad p)^2 / n_c(n_c \quad 1) \qquad (5\ 3\ 9)$$

and the "within children" variation

$$V_W \quad \sum_{j=1}^{n_c} E[C_j \gamma_D \gamma_{jH} / v(\gamma_D \quad \gamma_{jH})^2] / n_c^2$$

by

$$V_W \quad \frac{\gamma_D}{vn_c} [\frac{1}{n_c} \sum_{j=1}^{n_c} C_j \gamma_{jH} / (\gamma_D \quad \gamma_{jH})^2] \qquad (5\ 3\ 10)$$

Since the one-year study does not provide information about episode dura tion (5 3 10) has to be estimated from the daily home-visit study

5 4 AN EVALUATION OF STUDY DESIGN MEASURE AND ADMINISTRA TION

5 4 1 Problem identification

Planning the design of a community morbidity study based on a longitudinal series of equally spaced observations involves among other choices that of the interval between observations length of the survey and size of the study group Although there would theoretically be an infinite number of options these would in reality be considerably limited by practical circumstances such as the resources available for the study in terms of staff and economy or the community s acceptance of various procedures Other factors such as seasonal variation in morbidity or incomplete series of information and drop-outs would also have implications for the design chosen

Since in addition to the natural variation in morbidity within and between individual the technical design of the study will determine the precision f the morbidity measure this may be used as the criterion in rational choice of design as well as in the evaluation of data As practical circumstances seldom allow ideal solutions in terms of statistical precisions a realisti pproach would be to aim t an optimal yield of information within the frame of practically feasible options

Very little attention has been paid to the statistical implications of various study des gns in the morbidity studies eviewed in Chapter 1 Although similar to our one-yea morbidity survey in that data was collected at certain regular intervals over a ertain period of time most of them however aimed at a cont nuous measurement of morbidity as they also utilized information on illness occurrence as recalled by the respondents after ch in

terval Apart from some evidence given in reports from Guatemala and the USA (83 84) that parental recall of children s illnesses may result in sub stantial under reporting the reliability of this commonly used method does not seem to have been documented by any systematic studies In this study the collection of recalled information of unknown reliability was deliberately avoided Some data that would allow a comparison between recalled information with that obtained on daily home visits were however collected in connection with the supplementary study described in Chapter 4

An analysis of these data is included in the following statistical evaluation of the design of the one-year morbidity survey especially as the in tention is to contribute with some recommendations for design of morbidity studies in general With the aid of the statistical tools and criteria out lined in Chapter 5 1 5 3 we will attempt an evaluation directed towards questions like the following

- Assuming a morbidity study based on equally spaced observations how often should they be carried out and what would be the benefit of increasing *intensity* in home visiting?

  In view of the problems of *incomplete* series of observation and *seasonal variations* what *length* of survey should be chosen?

  Within a certain economical frame transformable into number of home visits what is an optimum allocation of *resources*?

- How does the accuracy of *recalled* information compare with that of equi distant observations and how does it vary with the distance from the day of interview?

5 4 2 Effects of changes in the intensity of home-visiting

Since visits in the Kirkos study were paid longitudinally to the selected households every fortnight the implication is that at most children were visited v L/ℓ 26 times The choice of fortnightly intervals was mainly based on rational considerations Weekly home visits were thought to be too frequent to be accepted by the community With the same resources twice as many households would be covered by home visits if the larger fortnightly interval was chosen thereby also increasing the expected number of dis covered illness episodes with a duration of more than one week

From the statistical point of view one might question whether this was an

optimum allocation of available resources How much would be gained by increasing intensity of home visiting? By means of the model suggested in 5 1 we may evaluate the theoretical implications and study the relative merits of changes in survey design

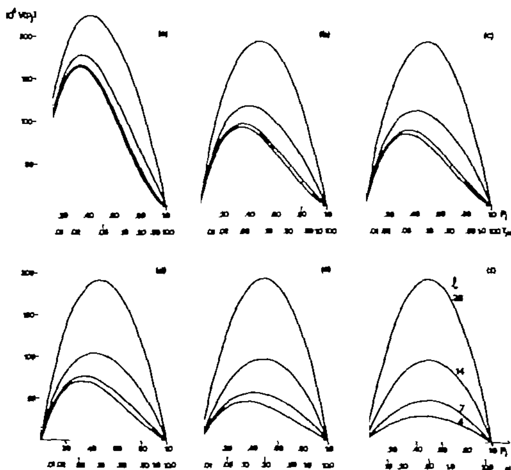


FIGURE 24 Variance f stimated individual morbidity pe year (5 3 3) a function f home-visit int nsity (ℓ) illness susceptibility (γ_{IB}) and true proportion f illness (P_j) The paramet γ_D recovery propensity was hypoth ti lly assessed (( ) ( ) and (f)) estimated from the daily home vi it tudy assumed t present t tal illne f ge group 0-23 24 59 and 60-143 months (( ) (b) and (d) espectively)

	( )	(b)	( )	(d)	( )	(f)
γ_D	0 05	0 0896	0 0988	0 1186	0 20	0 50

The role of the intensity in home visiting is illustrated in Figure 24 It shows for example that maintaining a one-year survey but changing t from 14 to 7 would for example in the case of a child aged 0 23 months and with a morbidity of P_j 0 40 decrease the variance (Figure 24 (c)) from 0 01148 to 0 00887 or in terms of standard errors of estimate from 0 1062 to 0 0942 i e by only 11 % This must be considered a marginal gain in precision not warranting a two-fold increase in resources Analogous calculations for a 24 59 and 60-143 months old child would give a 10 % and 12 % gain in precision respectively

Figure 24 also reflects the influence from the correction term in form of an assymetry with regard to the P-scale as t decreases This positive skewness is also a function of γ_D as can be seen by comparing (a) (f) in Figure 24 We thus gather that for low and moderate P_j s we get the lowest precision and the lower the value of γ_D i e the longer the episodes are the less is the relative gain from increasing home visit intensity while the opposite is valid for higher P_j s

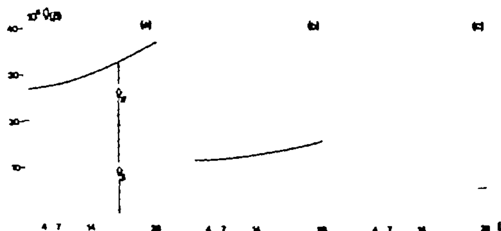


FIGURE 25 Decomposition f the v riance of estimated group morbidity (total illne) pe y gr (L=364) as functions of the intensity of home visiting (t) V_B and V_W denot th estimated va iation "between and "within child en

(a)	ge group 0-23 months	n 100	$\bar{p}$ = 0 2469	γ_D 0 0988
(b)	4-59	n = 186	$\bar{p}$ 0 1427	γ_D = 0 0896
( )	" 60-143	n_c = 286	$\bar{p}$ = 0 0505	γ_D = 0 1186

Sour : Tabl A9

Figure 25 illustrates for the three age groups the two variance components in $\hat{V}(p)$ as functions of t for fixed L v t 364 The rate of decrease

in variance as ℓ is lowered thus displays the gain in precision attained by more frequent home visits

It is obvious that the level of morbidity also plays a significant role but we may again conclude that increasing home visit intensity above that of fortnightly visits is hardly worthwhile Since the sampling error "between children" dominates the error variance the gain in precision in terms of standard error of estimate from a weekly design would be only about 3 % and a 95 % confidence interval would be shortened by 0 4 days in age group 0–23 months (Table 8)

TABLE 8 Standa d rror f estimated numbe f illne day pe yea by g group in one-yea study

		0–23	24–59	60 143
Age I months		0–23	24–59	60 143
	p	0 2469	0 1427	0 0505
	364 p̂	90	52	18
S E(364 p)	ℓ 28	7 06	4 71	2 94
	ℓ 14	6 43	4 31	2 72
	ℓ = 7	6 23	4 18	2 65
	ℓ 4	6 17	4 13	2 63
	ℓ 2	6 15	4 12	2 62
	ℓ 1	6 15	4 12	2 62

5 4 3 Effects of changes in the length of the survey

Due to mobility refusals absences or ther reasons (m) the length of the home visiting period usually differs between individuals Three aspects of the problem will be discussed below

For fixed intensities in home visiting how is the precision of estimated morbidity affected by a change in survey length?

For given sample of children how should available resources be llocated e what would provide optimal information to increase home visiting intensity or survey length?

A certain amount of drop-outs during the course of study is unavoidable due to the above reasons What degree of incompleteness sho ld be ac cepted?

For the individual measure p_j we get from (5 3 3)

$$\frac{V(p_j | \ell \quad L_1 \quad v_1 \quad \ell)}{V(p_j | \ell \quad L_2 = v \quad \ell)} \quad (v_2/v_1) \quad (C_1/C_2) \qquad (5\ 4\ 1)$$

where

$$C_i \quad [1 \quad 2 \sum_{v=1}^{v_i} (1 \quad \frac{v}{v_i}) \exp\{ v \ell(\gamma_D + \gamma_{jH})\}] \qquad i \quad 1\ 2$$

That is for a fixed space ℓ between visits the variance reduction gained by an increased length of survey is partially counter-balanced by an in creased autocorrelation as reflected by C_i Figure 26 shows the effects of lengthening the survey as a function of the number of visits and illness characteristics

It is evident that increasing survey length as well as home visiting intensity pays least for the healthiest ((a) (f) in Figure 26) and sickest child ((s) (y)) Furthermore within factual frames more is gained by in creasing the length of survey than by shortening the interval between visits.

Similarly for p we get from (5 3 6)

$$\frac{V(p | \ell \quad L_1)}{V(p | \ell \quad L_2)} \quad [V_B + V_W(L_1)]/[V_B \quad V_W(L_2)] \qquad (5\ 4\ 2)$$

where

$$V_B = \sum_{j \ 1}^{n_c} (p_j \quad p)^2/n_c(n_c \quad 1)$$

and

$$V_W(L_1) \quad (\gamma_D/v_1 n_c) \quad [\frac{1}{n_c} \sum_{j \ 1}^{n_c} C_j \gamma_{jH}/(\gamma_D \quad \gamma_{jH})^2]$$

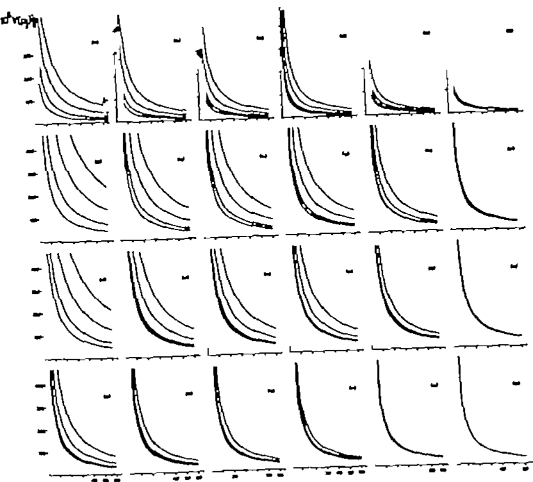


FIGURE 26 \ riance f estimated indi idual morbidity (p_j) function f the umbe of home vi its (v) and th i t rval betwee isits (t) f different combinations f γ_D and P_j (γ_D re very propensity pa ame μ_D mean pi ode d ration P_j true individual propo tion f illness)

γ_D		0 05	0 0896	0 0988	0 1186	0 20	0 50
μ_D		20	11 2	10 1	8 4	5 0	2 0
P_j	0 05	( )	(b)	( )	(d)	(a)	(f)
	0 25	(g)	(h)	(i)	(j)	(k)	(l)
	0 50	(m)	( )	( )	(p)	(q)	( )
	0 75	( )	(t)	( )	( )	( )	(y)

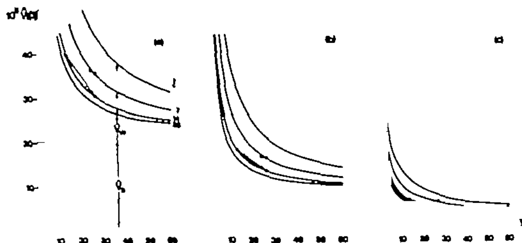


FIGURE 27 Estimated vari ce of g oup morbidity ($\bar{p}$) as function of numb r of home vi its (v) and spac between visits (ℓ)
(a) age group 0-23 months γ_D = 0 0988 (Source: Table A9)
(b) 2 -59 γ_D 0 0896
(c) 60-143 γ_D = 0 1186

In the choice between a one-year or 6-months fortnightly survey we can calculate

$$\frac{\hat{V}(p|\ell\ 14\quad L_1\ 364)}{\hat{V}(p|\ell\ 14\quad L_2\ 18\ )} \quad \frac{0\ 4\quad 9\ 8}{20\ 4\ +19\ 5} = 0\quad 6$$

i e a variance reduction of 4 % will be the benefit of a doubling of resources in this way (The corresponding figures in age groups 4 59 and 60-143 months will be 7 % and 5 % respectively) Figure 27 also indicates that 6 fortnightly visits during one year (——) should be chosen rather than 26 weekly visits during half a year ( )

The above aspects are presented purely from a theoretical point of view Clearly the administrative problems will increase with a longer survey On the other hand if seasonal variations are present (see p 83) a one-year survey is called for The choice of (ℓ v) (14 6) therefore seems quite satisfactory from a theoretical as well as a practical point of view

Formula (5 4) an also be useful when within a certain economical frame we want to determine the sample size What would be an optimum allocation should 00 children be visited 6 times each rather than 400 children 13 times? If the cost per interview is constant i e independent of whether

a person is reinterviewed or a new respondent is contacted the resources B could be written

$$B \quad n_c \, v \, b \qquad (5\ 4\ 3)$$

where b is the cost per home visit

If however there are initial costs associated with the individual (or the household) e g costs for finding the residence of the respondent costs for registration "costs" for establishing good contacts etc the remaining (v 1) visits being cheaper we may postulate a cost function like

$$B \quad n_c b_1 \quad n_c (v \ 1) b_2 \qquad (5\ 4\ 4)$$

where

b_1 initial individual cost

b_2 cost per subsequent visit

If e g 10 b_2 b_1 B $n_c v b_2$ $n_c(b_1 \ b_2)$ $n_c b_2(v+9)$ and

26 visits to 100 children would utilize the budget as fully as 61 visits to 50 children The statistical precision would then serve as the decision criterion

5 4 4 The p oblem of incomplete series of observation

In a longitudinal study a certain number of drop-outs cannot be avoided This is the third aspect concerned with the effects of a change in survey length In this particul r study however the question is what *degree of incompletene* should be accepted and how the analysis should account for the fact that not all children were home visited during the whole year Figure 28 shows the distribution of the number of home visits to the 749 children enrolled in the longitudinal study The large variations motivate a weighing procedure

One obvious approach would be to use v the number of home-visits as weights attached to p_j the individual measure and to calculate

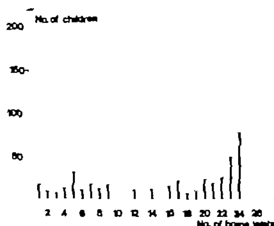


FIGURE 28 Di tribut n f the numbe of home visit t 749 child n
Source Table A10

$$\bar{p} = \sum_v vn_{cv}p_v / \sum_v vn_{cv} \tag{5 4 5}$$

as a group measure of morbidity where

n_{cv} number of children observed v times

p_v = average morbidity among children visited v times

In the case of large γ_D values i e short mean duration of episodes the weight function w(v) should equal v since the relative information contained in p_j given v_1 home visits compared to that with v visits is v_2/v_1 (see 5 4 1 and figure 29) The smaller the value of γ_D however the more will this weight function underestimate the relative importance of p_j given v_1 relative to p_j based on v_2 home-visits if $v_2 > v_1$

A comparison e g between $V(p_j)$ based on 26 and 2 visits respectively gives (γ_D 0 05 p_j 0 0)

$$\frac{V(p_j|v_1 \quad)}{V(p_j|v_2 \quad 26)} \quad \frac{v_2}{v_1} \quad \frac{C_1}{C_2} \quad \frac{26}{2} \quad \frac{1\ 95\ 2}{1\ 8360} \quad 8\ 9717$$

In the corresponding binomial case we get

$$\frac{V(p_j|v_1 \quad 2)}{V(p_j|v_2 \quad 26)} \quad \frac{v_2}{v_1} \quad 13\ 0$$

This means that the relative importance paid to p_j when $v =$ should be $(8\ 9717)^{1}$ and the weight attached should be $W(2)$ .6/8 9717 = 90 instead of 2 0 Similarly it can be shown that in a weekly design (ℓ 7) one has $W(2) = 4\ 61$ Since the proper weight function $W(v)$ approaches v as γ_D P_j and ℓ increases one might justify the use of $W(v)$ v as a weight function in the present study where γ_D 0 0988 0 0896 and 0 1186 are estimated from data in age groups 0-23 24 59 and 60-143 months respectively The use of (5 4 5) would then give the successively pooled variance estimates

$$V(p_k) \quad \sum_{v=k}^{26} v^2 n_{cv}^{\ 2} \quad V(p_v) \,/\, [\sum_{v=k}^{26} vn_{cv}]^2 \qquad (5\ 4\ 6)$$

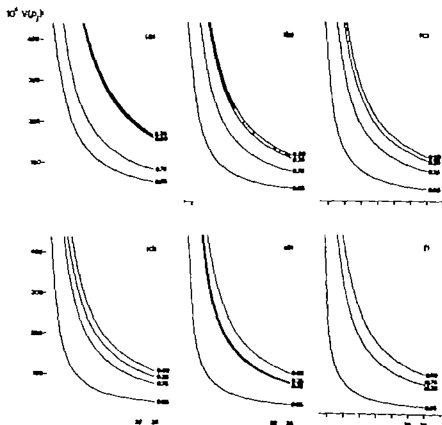


FIGURE 29 V iance f estima d individual morbidity (p_j) as func i f numbe f home visits (v) recovery propensity (γ_D) and true individual morbidity (P_j) when f tnightly de gn (ℓ 14) is employed

The rate of decrease in variance of p_j as v increases is displayed in Figure 29 for six increasing values of γ_D (decreasing episode durations) and four true illness proportions (P_j) Each combination of γ_D and P_j will then also correspond to a "recovery propensity"-parameter γ_{jH} $= \gamma_D P_j (1 P_j)$ where $1/\gamma_{jH}$ represents the individual mean duration of "health episodes

The increase in variance as v is lowered means that especially in the range $v < 10$ the corresponding p_j-values will be considerably imprecise and this must be accounted for in a simultaneous analysis

From Figure 29 it can be seen that as γ_D increases i e illness occurs with shorter durations the variance curves approach that of the simple binomial variance $P_j(1-P_j)/v$ It can be checked that for γ_D 0 50 they actually coincide This is also reflected by the circumstance that the curves for the symmetrically chosen P_j values 0 25 and 0 75 gradually approach each other



FIGURE 30 Pooled estimates f g oup morbidity (Total illnes) p and th rr ponding variance estimates by ge group (Sourc Tabl A10)

Figure 30 illustrates how p changes when individuals with successively fewer home visits are included and what will be the ultimate gain in precision with their inclusion Thus children with fewer observations especially in the younger age groups had somewhat higher morbidity rates than those

who were observed for the whole period There may be several plausible ex planations for this pattern Incomplete observation periods were for example more common among young children (Figure 32) mainly due to the higher mobility of households with few and young children (■) Declining morbidity because of increasing age is most apparent in this age group and possibly causing a higher $\bar{p}$ if children with short observation periods at the beginning of the study are included The higher morbidity among children who died during the course of the study would on the other hand only cause a marginal effect in this direction Only 5 deaths during the year were reported and these children belonged to different age groups (■)

Another explanation for the higher average morbidity among children with few observations is apparent from Figure 31 which displays the seasonal variations in morbidity The general pattern is that of a decrease in mor bidity during the one year study period Cons dering that an age classifica tion based on age as recorded at the baseline study in 1972 could partly

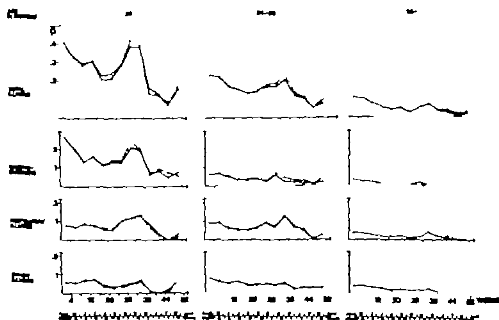


FIGURE 31 Se sonal va iations i morbidity ($\bar{p}$) by diff ent ag groups and ub-clas ifications f illnes
(—) ag lass ficatio based on g as recorded in 1972
(—) ag clas ificat on based on ge t the time f ob rv tion

have caused this pattern the morbidity rates were also calculated using children s age at each observation This however had only a marginal can celling effect on the general decrease Interviewer and respondent bias due to declining interest and cooperation respectively may possibly have con tributed but do not offer a full explanation for the general pattern as there are differences between age groups and illness sub-groups which would be more readily interpreted as true seasonal variations

Thus in the age group 0 -3 months the rate of gastroenteritis was highest in the beginning of the study period (April-May 1972) and in the middle of the study period (October-November 1972) The latter period also coincided with a peak of respiratory illness whoreas the stable rate of 'other ill ness showed a decline during some months before the end of the study period (January February 1973) In the other age groups apart from a moderate de-cline in general morbidity the peak observed in the middle of the study period (October-November 1972) seemed to be mainly due to respiratory ill ness

The attendance rates at the Outpatients department at the Ethio Swedish Pediatric Clinic (ESPC) Addis Ababa with around 100 000 visits/year (43) show a pattern that is similar to the general morbidity pattern observed in our study Unfortunately attendance statistics for the first half of the year 1972 are not specific with regard to diagnosis but during the following period a peak due to both gastroenteritis and respiratory illness was recorded in October November 1972 followed by a decline until rates again rose in March 1973 More detailed statistics are however available for the two preceding years During both 1970 and 1972 attendance rates by patients with both gastroenteritis and respiratory illnesses were highest during the months of March April and May A second smaller peak was ob-served in October-November The high morbidity rates observed in the begin-ning of our study and the peak observed in the months of October and November can therefore readily be explained as effects of seasonal variations The ESPC data also support the reliability of our observations that peaks of gastroenter tis and respiratory illness may occur simultaneously Reasons for the seasonal fluctuations in morbidity may partly be found in the cli matic conditions prevailing in Addis Ababa which in spite of its vicinity to the equator has a temperate climate due to the high altitude (about 7000 ft above sea level) with generally warm days and chilly nights The main precipitation occurs in the months of July September During February and March the so alled small rains occur followed by a period of warm and

humid weather which may contribute to the high rate of gastrointestinal infections during this time of the year

There are certainly no unique solutions to the problem of incomplete longitudinal series of observations One alternative would be to include all observations If γ_D is small e g in the range $\gamma_D < 0.08$ we should use a weight function that pays relatively more attention to p_j based on few observations than $w(v)$ v would do

When seasonal variations are present one should perhaps include only those individuals that were observed during most of the year conditional upon an optimum precision being maintained From Figure 30 it would thus be justified to use for instance v 17 as the point of truncation since the inclusion of more observations would not add substanti lly to the precision The use of $w(v)$ v as a weight function would suff ce in this range of v-values One should however carefully check whether the tendency for drop-out is correlated to some of the important variables under study

Figure 32 for example shows that an entirely different age composition than that in the original sample may be the result f the degree of incompleteness is related to the age of the child

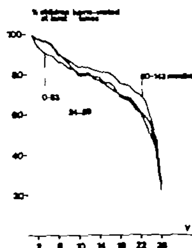


FIGURE 32 An illustration f the drop-out rate by g g oup (Sou Tabl A10)

If the decline in morbidity observed during the year (Figure 31) is neither due to seasonal vari tions nor to the ageing of the group of children but

is rather an interviewer bias effect one should consequently pay less attention to the morbidity observed towards the end of the period We are however not prepared to speculate about what weight function should apply in that situation

5 5 RELIABILITY OF MATERNAL RECALL OF ILLNESS

5 5 1 Background

The varying reliability of children s past medical histories as given by the parents is well known to most clinicians When mothers ability to recall their children s illnesses over a longer period of time - one to several years - has been systematically studied ([illegible]) considerable discrepancies have been shown between maternal information and that obtained from medical records Reviewing the problem of the layman s recall of medical events Kosa et al (77) point out that errors of recall are not simple functions of forgetfulness but tend to follow a complex psychologically motivated selectivity Comparing mothers reports on the use of clinical facilities during a period of one year they found that over reporting was more common than under reporting The magnitude of errors was greater for those who over reported and was also associated with a high number of visits.

Several of the longitudinal community morbidity studies reviewed in Chapter 4 have used parents recall at certain intervals during the study periods as the only or as a complementary source of information of illness occurrence but have often failed to discuss the problems of reliability However even when the recall period has been as short as 14 days ([illegible]) or 7 days (77) the recall has been shown to underestimate the rate of illness

As recalled information is a convenient source of continuous information on illness occurrence in a longitudinal study it was realized that the abstention from this method in the Kirkos study should be empirically justified This was organized in connection with the supplementary study described in Chapter 4 with the aim of comparing the degree of consistency between recalled morbidity information and that collected during a previous period of daily home visits

5 5 2 Field procedure

A separate survey was organized among households belonging to the supplo mentary study described in Chapter 4 Daily morbidity information was obtained from 67 mothers for 198 children during home-visits carried out during a 14-day period by three home visitors as described earlier On day 15 each mother was requested by another of the three home visitors to recall her children s illnesses during the proceding 2-week period She was first asked whether a particular child had been ill during the previous week and during the week before that and was then made to identify on how many and on which weekdays illness had occurred For each day during the 14-day period each child was thus recorded as *observed* (here = as reported on the daily home visit protocols) and as *recalled* ill or not ill A complete series of information was available for 183 of the 198 children For one child the mother could not recall whether he had been ill or not For 9 children recalled illness during the first week of the observation period and for 5 children during the second week could not be allocated to any specific day

5 5 3 Analytical procedure

In order to judge the consistency between the observational and [illegible] cedure we denote estimated proportions of illness calculated f [illegible] ber j with

$$p_{R_j} \quad R_j/r \qquad \text{and} \qquad p_{O_j} = O_j/r$$

respectively where

R_j = recalled number of illne days and

O_j observed

during a recall period of r days

The accuracy of an estimator is measured by its [illegible] error (MSE) around the true parameter value μ [illegible] biased estimato equal its ariance Generally

$$MSE(p_R) \quad E[(p_{R_j} \quad P_j)^2] \quad V(p_R) \quad bias^2(p_R)$$

An alternative decomposition would give

$$MSE(p_R) = E[(p_{R_j}\ p_{O_j})^2] + E[(p_{O_j}\quad P_j)^2]\quad ?E[(p_{R_j}\quad p_{O_j})(p_{O_j} - P_j)] \qquad (5\ 5\ 2)$$

where

$$MSI(p_R\ p_O)\quad E[(p_{R_j}\quad p_{O_j})^2]$$

estimated by

$$MSI(p_R\ p_O) = \sum_j (R_j - O_j)^2/n_c\ r^2 \qquad (5\ 5\ 3)$$

will be used as a measure of 'mean square inconsistency' between the methods If we assume the p_{O_j} is an unbiased estimator of P_j i e that $E(p_{O_j})\quad P_j$ and that $cov(p_{R_j}\quad p_{O_j}\ p_{O_j}\quad P_j)$ is negligible we would get from (5 5)

$$MSE(p_R)\quad E[(p_{R_j}\quad p_{O_j})^2] + V(p_O) \qquad (5\ 5\ 4)$$

From (5 5 1) it then follows that

$$bias^2(p_R)\quad MSI(p_R\ p_O)\quad V(p_O)\quad V(p_R) \qquad (5\ 5\ 5)$$

5 5 4 Results and interpretations

The analysis was undertaken to measure inconsistency between 'objective" observation and recall of illness with regard to the length and the position of the recall period (the time period for which illness is reported) Figure 33 illustrates the measurement procedure It should be noted that it shows how data were analysed and not the way the mothers were asked to recall illness since this would have required a much more complicated design Thus data were analysed for successively increasing length of the recall period (illustrated by arrows above the time axis) as well as for a recall period of a fixed length of three days (arrows below the time axis) with various positions in relation to time of recall

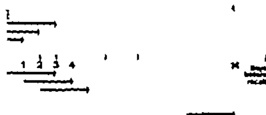


FIGURE 33 Ill tration f the recall analy is proced re Arrows denot length and po ition of the recall p riod

Figures 34 and 35 summarize the empirical results in terms of definitions from Section 5 5 3 for the two approaches in Figure 33

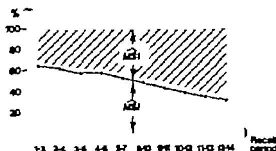


FIGURE 34 Degree of over- and under- ll by recall pe iod mea red by th ir relative contrib tion t mean quare inconsi t- ucy between re all d nd observed illne s
MSI⁺ E{[(p_Rj p_Oj)]²}/MSI(p_R p_O)
MSI E{[(p_Rj p_Oj)]²}/MSI(p_R p_O)
(Source Table A11)

It is interesting to note that the values of p_R and p_O being considerably deviant for short recall periods gradually approach as the length of the recall pe iod increases That this i a cancelling effect can be seen (Figure 34) from the fact that MSI (p_R p_O) the fraction of the 'mean square inconsistency' that measures the degree of overrecall decreases as the length of the recall period increases

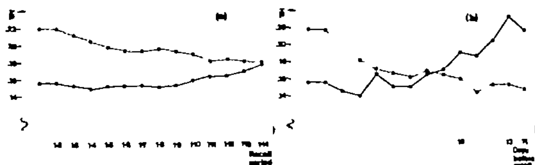


FIGURE 35 Compari on of obs rved ($\bar{p}_O$) and recall d ($\bar{p}_R$) illness by recall period ( ) and days befor call (b) (— = obs rved illne s — = recall d illnes) (Source: Table A11)

Plausible hypotheses would be that illness experience is recalled closer than it actually occurred or that recent illness is over-estimated while earlier events are to a large extent forgotten An apparent consistency between p_R and $\bar{p}_O$ in a commonly used 14-days recall (Figure 35) may thus conceal cancelling effects (b) that in the analysis of individual variations are confounding and may cause serious misinterpretations

CHAPTER 6

HEALTH DETERMINANTS — A SYSTEMS VIEW

6 1 INTRODUCTION

The Kirkos Project was intended as an exploratory study of a health system and its components (Figure 1) and was not organized to test certain prestated hypotheses This does not imply however that an analysis of this system is possible or even meaningful without some basic hypothetical and theoretical assumptions The basic notion that child health may be conditioned by the social and the bio-physical environment as well as by facilities in the health service sector and that equal attention should be paid to factors from these various fields guided the choice of variables and will also determine the strategy of the further analysis

The previous chapters have concentrated on the definition and measurement problems with regard to acute morbidity and we have now reached the stage when we can study a measure of acute morbidity as a criterion variable against several sets of predictor variables representing various aspects of the child s socio-environment In this system causal as well as spurious associations may occur on diff rent levels between factors that may also interact in their effect on child health This makes the evaluation of the relative importance of the various factors an intricate problem conceptually theoretically and methodologically It may therefore be necessary to consider in more deta l the general research context within which this study was undertaken as well as the theoretical aspects of creating models for health systems as a prelude to a strategy for the analysis of data

6 2 HEALTH MODELS

As we pointed out in the introduction recent medical literature has advocated the necessity of viewing health in relation to all factors in human ecology with an open mind to the possibility of finding "non-medical solutions to medical problems (**) The sparse studies carried out with this basic philosophy have however been limited both with regard to their general scope and their methodological sophistication

Referring to the rather abundant recent studies on health care Tilquin ([illegible]) points out that a systems approach has rarely been adopted Thus a multitude of complex relationships have often been ignored while the study has been concentrated on only a part of a system often bypassing the conceptualization phase going directly from reality to formal models which thus developed are further from reality than the ones which could be deducted from a generalized conceptual model through successive elimination of those aspects which cannot be formally accounted for and therefore clearly defined ([illegible]) This criticism can also be directed against the medical studies which examine general health measures in relation to socio-environmental factors

Jenny ([illegible]) proposes an ecological model of factors affecting dental conditions considering a hierarchy of systems of importance for dental health the oral cavity the individual the family and the community which are also claimed to constitute different legitimate levels for the prevention of dental disease

A WHO committee discussing indices of family health ([illegible]) emphasizes that the family is the basic bio-social unit and that health should be studied both with regard to individual family members and to the family in its entirety in relation to its biological social and economic roles Viewing community health in terms of qualities of the families of which the community is composed Miller ([illegible]) sees physical health and social interactions in the family as conditioned by many variables such as genetic inheritance and age parental education and ethnic economic state cultural values and the utilization of external services These approaches are basically systems-oriented although of limited theoretical scope

A systems theory approach in the field of environmental health is presented by Schaeffer ([illegible]) with the basic view that "just as man-environment relationships encompass practically all aspects of man s b ological and social life interventions to promote health can conceivably involve a multitude of different actions to be undertaken by the community" and also that environmental health objectives must be assessed in relation to other social goals Defining a system as a set of elements so related that change in the state of any element induces changes in the other elements Schaeffer points out that the researcher is free to set the level of the system and to include components in accordance with the problem to be solved and with the objectives of the analysis Man both as an individual and as a community member is the focal point for consideration The immediate family system is how-

ever not only part of an environment consisting of larger social groupings but it also exists and functions in relation to other types of systems that contain agents that affect his health Thus agents in the physical environ ment (physical chemical and biological sets of elements) and societal fac tors (social political economical and cultural element sets) may affect man s health through various pathways and interactions either directly or indirectly by their ecological and economic effects which in turn may inter act with or reinforce exposures and effects on human health These effects depend on intervening variables or host factors representing his relative resistance susceptibility or adaptability to environmental agents Schaeffer then details the components in these conceptual sub-systems of environmental health and explores the intervention points that are potentially available for control of environmental health problems

For the purpose of this study we propose that a health system may be seen basically as a social system with different levels of organization At the basis we are concerned with the health of the individual who usually belongs to a family or a household system which n its turn is part of a larger societal system or systems These systems are open systems in the sense that they may be influenced by other systems which may overlap with the social systems Health on both the household and the individual lev ls may therefore be affected by the phys cal and b ological environment the political system the econom system the educational sanitary and health care facilities offered or organized by the society The health of the individual may be affected by the economic st tus of the household its educational and cultural level its behaviour with regard to sanitation and illness and its use of health care facilities as well as by the bio-physical environment as it is encountered on the household level Intervening factors may operate on the different le els modifying the responses to agents in the external systems Households may for various reasons respond differently to inputs from the social and bio-phys cal environment just as individual responses to exposures may ary for instance acco ding to age and sex Furthermore we assume that var ous forms of nteractions take place on different levels in the system down to the indiv dual in whom health responses may interact with xternal factors to pave the way for other health effects This systems formulation of a health model is displayed in Figure 36

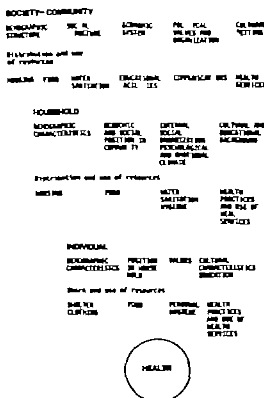


FIGURE 36 Determinants of health
– a social systems view

6 3 A CONCEPTUAL MODEL OF CHILD HEALTH

Models of child health have mainly focused on different interacting conditions on the household or family levels Some models for probable chains of events that may lead to protein–calorie malnutrition in a pre–industrialized country suggested by Craviloto (m) may be given as examples He proposes that one pathway may lead from low purchasing power barely enough to cope with the necessities of life This would limit investment in environmental sanitation which in turn would maintain traditional concepts of health and disease including the lack of understanding of the nutritional needs of infants The lack of surpluses may also lead to early school leaving which establishes a feed back mechanism to technological backwardness and the persistence of primit ve concepts of health and disease Early school leaving

would also lead to early marriages between equally uneducated spouses thus multiplying the risks for inadequate child care illness and malnutrition The persistence of primitive conceptions of health and disease may also result in insufficient awareness of the hygienic requirements of the child Poor cleanliness would lead to a high frequency of infections which directly or indirectly cause malnutrition The increased morbidity would in turn lead to increased expenditure on health services which would further diminish the purchasing power

It is within a setting of this kind of interacting and inter related factors influencing child health directly or indirectly that we measured variables representing various aspects of the households and the individual children in the Kirkos area A systems approach was manifested by our attempts to organize the study on an inter-disciplinary basis and by the aim to search for determinants for child health among a wide set of variables on different levels in a health system. We have a special interest in the factors which may prove to be associated with pathways for intervention to improve child health The fact that we are not merely interested in the predi tion of health for individuals or groups of individuals means however that *information about the predictive powe of various factors is f limited use to us if we cannot relate it to the causal tructure of the sy tem.*

Even if our approach is an exploratory one aiming at the generation of hy potheses the int rpretation of our data is obviously impossible without some basic theoretical assumptions about the levels on which different factors operate and about their degree of logical pri rity in relation to the cri terion variable Figure 37 displays the main components of a conceptual model of a child health system which we have already described (m) as directing the choice of variables in the Kirkos project Here we have also added an indication of the level of organization to which these components belong and an indication of thei order of priority in relation to child health In the study variables were only measured on the household and the individual levels In the model we have however also indicated components on the societal or community levels as the family characteristics would partly be an effect of the social and environmental conditions in which these households l ve

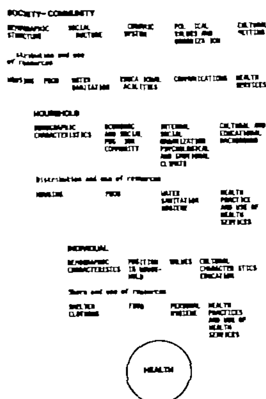


FIGURE 36 Det rminants of health
- ocial systems view

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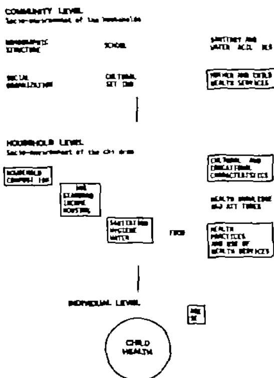


FIGURE 37 Component i a conc ptual model f child health Th model indicates a as wh re i f rmation wa sought in the Ki koe p oject ([ ] a as wh w us f l meas re we btai d On the househ ld level th ord of th omponents indi at th as umed degree f l gical pri rity in relation to hild health mea d n th individ- ual l l

6 4 ANALYTICAL APPROACHES

Models of causal chains in epidemiological research are always over-simplifications that represent only a fraction of the reality' Furthermore " the whole genealogy may be thought of more appropriately as a web which in its complexity and origins lies quite beyond our understanding Fortunately it is not necessary to understand causal mechanisms in their entirety to effect preventive measures Knowledge of even one small component may allow significant degrees of prevention' (84)

In epidemiology causal association has been defined (**) as "an association between categories of events or characteristics in which an alteration in the frequency or quality of one category is followed by a change in the other" The problem of making causal inferences on the basis of non-experimental data (**) is however not an easy one Here it may suffice to point out that a statistical association between two events by no means implies a causal association and also that causal associations may be indirect or direct It may also be wise to keep in mind that even in experimental studies the causal nature of the relationship between two events can never be decided with absolute certainty

> *Clearly a causal relationship between two variables cannot be evaluated empirically unless we can make certain simplifying assumptions about other variables It is because of this hypothetical nature of causal laws that they can never be tested empirically in the strictest sense of the word since it will always be possible that some unknown forces may be operating to disturb a given causal relationship*
>
> *Generally speaking the greater the departure from the ideal experiment and from completely isolated systems the larger the number of variables that must be explicitely brought into the causal model And the larger the number of such variables the simpler our assumptions must be about how they fit together We must therefore pay a considerable price whenever we find it impossible to experiment or to study isolated systems (**)*

A comprehensive statistical analysis of non-experimental data from a child health system as postulated above calls for multivariate approaches which allow simultaneous interpretations of interaction patterns among the variables Studies of child health in relation to socio-environmental background factors while recognizing the multivariate nature of the problem have often failed to consider this in the analytical phase of data processing which has often not been carried beyond the search for bivariate associations with frequent use of statistical significance tests These have sometimes even been considered informative with regard to the relative importance of the predictors (**) The assumptions behind such a practice which is not uncommon in medical research must obviously be that statistical significance is equated with importance in a clinical practical or causal sense (**) The frustration felt when trying to extract relevant information from the data made us gradually aware of the necessity to reconsider the role of statistics in general in the generation of knowledge

Anything may be significant in the statistical sense it is merely a question of sample size which becomes quite evident when the basic logic of

tests of significance is considered the larger the sample the less chance there is that the observed event is simply a product of sampling error It may however be a useless and even misleading finding a point which was recognized long ago in a polemic with the classical statistician Karl Pearson (112)

> *the operation of the factor of chance is not by any means the most serious cause of fallacy in medical statistics I am confident that medical statistics are vitiated much more seriously by a want of conformity between test cases and the 'control cases uncertainty of clinical diagnosis carelessness untrustworthiness or ignorance of individual observers* (140)

On the other hand a non-significant result may well be clinically significant or determinate the finding that there is no statistically significant difference between the effects of a cheap treatment and an expensive one may actually determine a course of action that of abandoning the expensive one until further evidence motivates it

Moreover it should be obvious that a finding is always significant *relative to* a null hypothesis which should originate from a sound theoretical groundwork There is nothing more simple than finding a hypothesis that can be falsified in fact there is an infinite number of them but in order to be able to judge etiological importance and statistical significance simultaneously it is worthwhile to spend some time and effort on a synthetic review of literature This is one part of the exploratory hypothesis-generating phase of the research process that is often either not reported or is simply lacking in development studies from the socio-medical field

When trying to "understand" his findings the investigator pays additional attention to the answering of questions not originally posed The testing of hypotheses on the very data that generated them is of course totally inadequate and such data dredging may provide fallacies if used as a deductive tool in the process of generali ations We should note again that a statistical significance test does not tell us whether an association is an important one Moreover it can never tell us that the association *did not* occur by chance At best they can tell us that it is unlikely that it did so Although a statistically significant result is *one* evidence for rejecting the hypothesis under test *a non-sign ficant result is no evidence of ts tru h*

This study can be classified as multivariate since it aims at the identifi cation of associations between several sets of variables In an extensive body of available techniques the choice of an appropriate method will indeed require criteria A more or less pronounced 'ad hoc'-strategy may otherwise be the result guided mainly by the access to certain computer programs Multivariate data means that simultaneous measurements have been collected for each sampling unit and/or unit of analysis The multivariate method is a tool for studying a set of variables selected on theoretical as well as empirical grounds in a given system to see whether certain variables con tain in principle the same amount and type of information and with the ulti mate aim of predicting what will be the effects of changes in some of them

Non-experimental research is almost exclusively performed in indeterministic systems and whatever statistical technique is used there will always re- main a certain portion of unexplained variation It is also characteristic of non-experimental studies that for ethical or administrative reasons the study units cannot be randomly exposed to the hypothetical etiological factor or intervention measure but have to be and should be observed in the natural community setting This is also why the validity of any causal in- ference rests heavily upon the degree of accomplishment of a "dialogue" between the prior theoretical knowledge and a systematic treatment and interpretation of empirical findings

We also have to take into account that 'explained" variation does not neces sarily permit causal interpretations and may at least partially be an artifact We believe the right approach when interpreting empirical findings and also a prerequisite in the choice of method is a proper balance between clinical judgement and statistical methodology (m) rather than the "objec tive search for statistical significance This is best achieved in an epi demiologic study by a continuous xchange of points of view (read "struggle") between the medical research worker and the applied statistician

The non-experimental tudy in the public health field must control for con- founding factors Confounding may result from multicollinearity i e the explanatory variables intercorrelate and substitute for each other in the statistical sense thereby mak ng t difficult to assess their relative im- portance This is partly a statistical problem that multivariate methods handle more o less efficiently (n m) but to a large extent also a valid- ity problem. Variables carefully validated and cross-checked should be chosen to represent conceptual components in a postulated model rather than

what is the case in the opposite common phenomenon a variable being revealed as important by the analytical instrument But what concept does it represent taking into consideration the way it has been measured?

Confounding may also result from the assumptions usually made of additive effects There are strong reasons to believe that interactions i e the effects from one variable varies with the levels of another are even more important in social and medical sciences than main effects and that it would often be misleading to look for overall gross effects Especially if the ultimate aim is to propose action programs which may lack considerable efficiency when interaction effects are ignored

> *The fact that the theoretical constructs in which we are interested are not the same as the factors we can measure nor even simply relate to them should affect our analysis techniques and focus attention on creating or locating important interaction effects to represent these constructs"* (xx)

Multivariate analysis should not be confused with the improvised method of 'put it all in and we ll see what we ll get out of it The necessary preparatory work should impose some restrictions on the process in order to make it manageable (xx) If the guess-work state of knowledge has been passed the postulation of a model may be needed to account for some substantial parts of data heterogeneity This however should balance with the less practical applicability that may be the result of a complex model In the exploratory phase of theory building it may be necessary to study the intercorrelations between the variables within the conceptual components in order to describe the total variance in a sample in fewer dimensions thereby reducing the number of variables while minimizing the loss of information This may be achieved by means of principal component analysis where the dimensions are constructed as linear combinations of the original manifest variables in such a way that they successively account for the major independent patterns of variation in the sample

The difficulty with such mechanical methods however is that they in fact only recognize the structure of interdependence Two highly correlated factors may influence the dependent variable in quite opposite directions and a more or less interpretable combination of them may even cancel both effects. Multiple regression techniques may satisfactorily handle intercorrelations between predictors but rest on the other hand quite rigidly on the assumptions of additivity linearity and metric data qualities

The choice of multivariate method is mainly guided by the problem as identified verbally in medical terms and translated into a more formal statistical vocabulary The purpose may thus be to *construct models* for predictive purposes (multiple regression) and causal interpretation (path analysis) to *predict group belongings* by finding linear combinations of the variables that maximize differences among pre-existing populations (discriminant analysis) *to sort* a previously unpartitioned heterogeneous collection of objects into a series of sets (cluster analysis) *to arrange* the objects graphically in few dimensions (non-metric scaling) *to reduce dimensionality* of data (principal component analysis) to resolve the intercorrelations among variables by *searching for latent structures* (factor analysis) or to *search for structure* in data homogeneity association and interaction patterns (AID-analysis) The above purposes are clearly complementary and most studies may thus benefit from a joint use of more than one method

Having specified the problem the postulated dependence between and within conceptual components is a further criterion guiding the choice of method In the classical *unidependent* model we aim at explaining variation in an explicit *(well defined and observable)* criterion variable by means of a set of background factors (predictors) while there is no explicitly stated criterion variable when studying *interdependence* If there is more than one criterion the *multidependence* may be stud ed in path model or via latent new dimensions as canonical correlations

Finally the metri qualities of data *introduce more or l ss mportant meth*odological restrictions (s ss ss ss) The fact that a variable has got high metric quality does not however necessarily mean that it will act like one

In the following chapter we will adopt a two-stage strategy for the data analysis In the first stage a search device will be used to structure data by finding variables that work (ss) in the sense of being as unidimensional representatives of the r conceptual component s possible This stage will thus search fo associations and interaction patterns for later use in the second stage where we will attempt to approach a causal interpretation of postulated models

CHAPTER 7

A SEARCH FOR ASSOCIATIONS AND INTERACTIONS

7 1 A REPRESENTATION OF THE CONCEPTUAL MODEL OF CHILD HEALTH

The Kirkos study provided information on a number of variables which represent some of the components in the proposed model of child health (Figure 37) As has been mentioned in 2 2 information on household characteristics were based on cross-sectional data obtained during the base-line study in 1972 whereas children s morbidity and weight development were prospectively recorded on the fortnightly home visits during the following year A special cross-sectional study furnished data on the prevalence of intestinal parasites and data on clinic utili-ation were obtained during a follow-up study one year after the base-line study

A detailed description of the survey procedures and of the variables for the whole sample of 600 households and 1020 children under the age of 12 years is given elsewhere (w) In the following brief comments we intend to give a presentation of the variables as representatives of the components in a child health system Table A12 gives a review of these variables which were all measured on the household and on the individual level in an urban community where a large proportion of the households were underprivileged living under or near the subsistence level of standard in surroundings characterized by poor housing and sanitation We do not claim to have measured a complete set of variables reflecting the components that we would like to include in a model of child health Thus for instance we were not able to organize the collection of reliable data on food availability and consumption Some information of this kind was however obtained for a small part of the households but is not listed here because of its incompleteness

The 1020 children belonged to 411 of the 600 households in the original sample To obtain a manageable number of households to be followed by longitudinal observations and because of our particular interest in young children we aimed the home visit study at the 346 households that had at least one child under the age of 7 years When this study started 298 of these households were still available but due to refusals and mobility a further 21 households dropped out leaving 7 households with 749 children as the

actual study group. Tablo A12 gives the frequency distributions by variable class for households and children in this group and the original group of 411 households Due to the criteria for selection there is a slight over-representation of housoholds with young children in the study group which also has a slightly lower proportion of households with few children mainly because of tho higher mobility noted among households of small size (*) These differences should be born in mind in the interpretation of morbidity data when the question of inference arises with regard to the population of the community The similarities in other respects however favour the idea that this can be done with some degree of safety

With regard to household composition all persons eating and sleeping in the household have been counted as household members including relatives and servants In the majority of households two parents were present In a few cases a female guardian other than the biological mother has been counted as the mother The household with a single parent consisted except in one case of a single mother and her children

Information on household income was not easily available and was partly based on the home visitor s intimate knowledge of the families who could thus be classified into some income-groups Families under the level of 100 Eth $/month may be regarded as underprivileged as t has been claimed that an income under this lovel in a family of 5 members does not allow for the purchase of an adequat amount of food (*) The large variation within this group motivated a further sub-division which was set at 50 Eth $/month. A daily labourer for instance seldom earnod more than 1 Eth $ a day The minimum starting salary of a university graduate was 500 Eth $/month which can be considered as the lower income limit for the privileged Similar dif ficulties arose when information on the cost of housing was collected Most households paid rent but a cons derable proport on of them owned their house or had it on lease For these households there was no available method of calculating the cost

The number of rooms and the living area were considered to express different aspects of crowding Living area per household member was classified into two extreme and two middle classes pproximately following the 10th 50th and 90th percent les Variables expressing housing quality walls floor ceiling etc have been d vided i to two groups that reflect an inferior and a better quality Other character stics such as roofing and lighting were also recorded but are not included here as there was very little variation

between the households

The majority of the households got their water from private or shared taps or by buying from neighbours The water pipes often passed close to the sewage ditches in the streets which would make the quality of the water very questionable Some people fetched their water free of charge from a stand pipe that belonged to the nearby railway station Approximate information on water consumption in the households ([illegible]) is given per household member The classification was made according to the same principles as for Living area Most households used pit latrines that were either private or shared among several households Especially in the latter case they were of a very low hygienic standard This was also true of the public pit latrine used by a number of households

Marriages between spouses of different ethnic groups existed to some extent Here we have used the ethnic group of the mother as a variable Different household members usually belonged to the same religious denomination and we have therefore classified the households according to the religion of the head of the household Education was recorded separately for fathers and mothers who were classified into illiterates those who were able to read (and sometimes write) without having attended any formal school and those with some degree of formal education (varying from elementary school to university education in a few cases) This classification has been discussed in more detail elsewhere ([illegible])

The base line survey also included questions which were supposed to reflect attitudes and knowledge in health and disease The respondents were for instance asked whether they knew about the possibility of preventing a child from getting tuberculosis smallpox whooping cough and tetanus The number of these illnesses for which they claimed knowledge about vaccination was then used as a measure of this variable The answers were however affected by a certain guess rate ([illegible]) Special interest was taken in beliefs and practices concerning measles which is widely held to have supernatural causes thereby often leading to the avoidance of medical care (54) A mother s opinion about the cause of measles may thus reflect her degree of traditionality but as many mothers did not state an opinion their answers can hardly form the basis for a measure of this variable Many of the mothers claimed that they would take a child severely ill with measles to a clinic or to a hospital even if they expressed a traditional opinion about the cause of measles

The respondents willingly volunteered information if their children had undergone the common traditional practices of uvulectomy (usually performed by local medical men often in connection with acute throat infections and without any hygienic precautions) tooth extraction (of the first milk tooth) and circumcision and clitoridectomy for boys and girls respectively (m) Although information was obtained for individual children these variables have been listed among the household variables as they result from the behaviour of adult household members

The questionnaire included detailed questions about the children s vaccination history However only the initial question whether a child had been given any vaccination or not was consistently answered Information on children s utilization of the MCH-clinic that was introduced in the area was obtained from the mothers during the follow-up survey This question was directed to mothers only some of whom were not present on this occasion, which is part of the explanation for the considerable proportion of non-response

The age classification of the children was based on information obtained at the base-line survey in 1972 The consistency between thi information and age information obtained one year later was shown (m) to be good in the youngest age groups but progressively poorer in the older children This however only had a limited effect on the consistency of weight for age measures based on the two age recordings We have here used weight for age as recorded at the base-line survey in 1972 This is expressed in % of the Harvard Standard (70) and taken as a measure of the nutritional status Intestinal parasites were studied during a cross sectional study based on the examination of one stool specimen per child in the middle of the longitudinal study period.

These are the variables that may be used to represent some of the components in the child health system postulated in the further analysis of acute morbidity As we have indicated above these variables vary with regard to their closeness to the component they may express in reliability completeness and interpretability Before the final selection of explanatory variables it may however be wise to consider the assumptions behind feasible multivariate methods and their implications for data analysis

7 2 STRUCTURING DATA STRATEGIES AND OPTIONS

7 2 1 Basic procedures

The use of multivariate statistical methods in the analysis of extensive sets of ecological and individual factors for the importance of health is now well recognized although these methods have rarely been applied in surveys from developing countries where data collection presents special problems ([illegible]) In the present study the limited possibility of obtaining quantitative information has for instance led to a frequent use of categorized variables Conventional multivariate techniques such as multiple regression analysis are difficult to apply to "soft data because of their built in assumptions about metric qualities linearity and additivity Methods have therefore been called for that impose less restrictive assumptions on data but that may still be useful in an exploratory hypothesis-generating stage of the research process ([illegible])

One technique which has found increasing use in socio-medical research is the AID (Automatic Interaction Detector) method ([illegible]) This method and its supplement the THAID version (104) which are applicable to the data furnished by this study are exploratory methods for the classification of individuals into disjoint homogeneous groups with regard to a criterion variable These groups result from separate as well as interaction effects in the 'explanatory' variables which should either be categorical or categorized The AID version requires a metric criterion variable i e it should be at least intervally scaled while the THAID method was designed to handle the nominal case

The sub-groups in the AID analysis are constructed through a stepwise application of one-way analysis of variance techniques where the original sample is sub-divided through a series of dichotomous splits (Figure 38) The criterion for these successive splits is to select at each stage the explanatory variable which results in the greatest between-groups sum of square

$$BSS = \sum_{i=1}^{2} N_i(\bar{y}_i - \bar{y})^2 = \frac{N_1 N_2}{N_1 + N_2}(\bar{y}_1 - \bar{y}_2)^2$$

The predictor is chosen which gives the maximum reduction in total variation, i e which results in the largest

$$BSS/TSS = \frac{N_1 N_2}{N_1+N_2} (\bar{y}_1 \quad \bar{y}_2)^2/\Sigma(y - \bar{y})^2$$

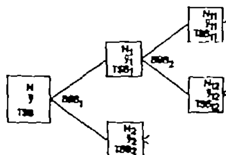


FIGURE 38 A schemati desc iption of the AID method
N group siz
TSS tot l sum f square
BSS between group sum of square

It can be shown that the BSS/TSS criterion used by the AID programme is equivalent to finding the predictor variable which after a division of its classes into two halves through an indicator variable gives the maximum squared correlation coefficient between this indicator and the dependent variable To warrant further sub-division i e for a split to be considered as important it should reduce the "unexplained" variation with a certain predetermined fraction of the original variation and not construct groups of small sizes When these restrictions are no longer met there is no explanatory variable powerful enough and the hierarchic "tree" process terminates

While the AID method uses a group mean to "predict" behaviour the THAID version focuses on the distribut on shape of the criterion The sequential partition is analogous to that in AID but in view of the lacking metrics in the dependent variable variance reduction would be an improper split cri terion There are two optional statistics replacing the BSS/TSS criterion The *Theta-statistic*

$$\theta_{y/x} \quad \sum_{i=1}^{2} (\frac{N_i}{N})(\frac{M_i}{N_i}) \quad (M_1 \quad M_2)/N$$

expresses the sum of products of the probability of being in the i^{th} group and the probability of belonging to the modal class with frequency M_i Thus

the binary split of x is chosen that maximizes the sum of the two modal frequencies The *Delta-statistic*

$$\delta_{y/x} = N_1 \sum_{j=1}^{G} |P_j - p_{1j}| + N_2 \sum_{j=1}^{G} |P_j - p_{2j}|$$

choses that dichotomy where the weighted probability distributions over G classes differ maximally from the original group and hence from each other

7 2 2 Rationals for and limitations with the AID method

In an original article (xx) Morgan and Sonquist motivate the need for data scanning methods as preliminaries in social surveys

- the complex multivariate nature of data and the world from which they come
- the classificatory nature of most measurable entities
- the fact that not only the dependent variable involves measurement errors (a common assumption)
- the complexity of the sampling procedure (far from simple random which is the routine assumption behind most statistical techniques)
- the non-additive nature of social phenomena where "we may have inter action effects not because the world is full of interactions but because our variables have to interact to produce the theoretical constructs that really matter"

There are however several limitations with methods like the AID and even dangers if it is used uncritically and the intuitively appealing visuality is perhaps one of the major weaknesses the reader of an AID-tree is so easily attracted by its beauty that he does not feel he needs or dares to examine the soil or the fertilizer

Since groups rather than individuals serve as units of analysis large samples are required often unrealistically large The AID-method may well serve as a segmenting device in the formation of target groups but its predictive power in the numerical sense should not be exaggerated Each group is characterized by its mean value size and dispersion The fact that an arithmetic mean often pays too much attention to extreme values motivates caution against skew distributions in the dependent variable A THAID-analy-

sis may after suitable categorization of the dependent variable or a transformation be preferable since the AID analysis tends to split off small groups with extreme values without any corresponding logic in the theoretical constructs (m4)

Multicollinearity is not handled by the method Thus predictors may substitute for each other and the order of appearance in the tree is no indication of the relative importance of a variable which may rather reside in its interpretative role in the causal process

Since the AID method has a strong tendency to capitalize on chance variation it is wise if possible to validate the results This is not a matter of looking for statistical significance but rather an investigation of the robustness and stability of the process (m) Cross-validations may for instance be achieved through a split-half technique where separate analyses are conducted on each of two random partitions of the sample

More often than not there is one concomitant variable (in our case the age factor) that dominates among the 'explanatory' variables not because it is the most important causal factor but because it is strongly associated with the phenomenon under study and thus has to be controlled for By letting it compete with other predictors the material would then obviously be reduced so much that we would just end up with a "so what? -statement By including it as a covariate the analysis could alternatively be set up to maximize either differences in the slopes of the regression of the dependent variable on this covariate or differences in explained variation due to regression (means and slopes)

Since every social phenomenon under study is a process in several dimensions a conceptual model may serve the purpose of defining logical priorities among the variables One can therefore preferably preform the analysis in stages where the effects of the variables which are closest to the criterion variable are not analysed unt l some of the predisposing factors have been accounted for Technically this may be achieved by using the residuals (deviations from group means) from the first stage as dependent variables in a second stage or by the stepwise introduction of sets of variables which may produce furthe dichotomies within each of the groups that result from the previous step (ranking options) The latter approach is more appropriate if the different sets of va lables are thought to interact

It should be emphasized that automatic scanning devices like the AID method should be interpreted as such and not as tools for generalization purposes They should be used to *structure the sample* and not for the purpose of making inferences about some unknown or vaguely defined population Properly used they may be rational instruments which can aid in the understanding of the underlying causal process

7 3 SELECTING VARIABLES THAT WORK

In section 7 1 we have accounted for the variables that were measured during the course of the project In order to secure the selection of meaningful variables for the multivariate analysis of acute morbidity it is however necessary to scrutinize them with regard to their completeness and the extent to which they are well defined as representatives of certain components concepts or dimensions as well as to whether their potential associations with the criterion variable would be available for interpretation As the AID methods do not account for the multicollinearity problem it will also be useful to pay some attention to the intercorrelations between the variables especially in the cases where several variables represent similar aspects of one component It may for instance be wise to choose only one of several strongly associated sub-components as an explanatory variable

The variables listed under Household composition (Table A12) are relatively uncontroversial as descriptive attributes of the households However as children under the age of 5 years are more frequent introducers of infection into the households than older children (Table 6) we have taken this as a motive to select Number of children under 5 years excluding the total Number of children under 12 years as an explanatory variable

The Household income variable presents some interpretation difficulties If the households are given the mid-point values in each of the income classes it is possible to calculate the per capita income (Table A13) The wide variations give the impression that per capita income would be a more precise measure of household income level This may however be misleading as many households were known to have extra income in kind although it was not possible to obtain exact information about this It is also doubtful whether the cash income would equally benefit the different members of a household We have therefore kept the original variable which classifies the households with regard to the total income level keeping in mind that

this may not necessarily reflect the total resources of the household but perhaps rather its social and professional status

The possibility of including Cost of housing as an explanatory variable is hampered by the fact that there is a large group of households those who owned their houses for which this information could not be obtained It can be shown that there is a positive association between cost of housing and the other variables which express quality of housing and that most of the privately owned houses are among the better ones As the other variables Living area/household member Number of rooms/household Type of floor ceiling walls and windows express different aspects of the standard of housing it will be unwarranted to retain the cost of housing as a general measure of this standard especially since it is incomplete and as it may cover the effect of the other variables We propose Living area/household member and Number of rooms/household as two measures of crowding The latter must then be related to the number of household members Unfortunately the number of rooms in households with more than two rooms were not recorded It is however possible to arrange the households into two groups. Considering the households with 3 rooms or more those with 9 household members will have a maximum of three persons per room We have arbitrarily chosen this limit to group the households with regard to a high or a low number of persons per room apart from a small proportion of the households for which this information was not available This i naturally a very crude measure of crowding especially since we have not studied how the various households used their rooms The measures of quality of floor walls ceiling and windows are all positively associated We have selected Type of floor as being potentially health related If floor consists of the bare ground it is difficult to clean and there will be increasing risks for children to contract infect on by faecal contamination Since the other variables show their strongest associations with Type of floor it may also be justified to use it in the place (Table A14)

Water consumption va ies to some extent with Sourc of wat r (Table A15). Thus there is a rel t vely l ge propo tion f households with a high consumption among those with private water taps If however the quality of water varies with the source of wate this may eithe exaggerat or diminish the health effects from the amount of wat onsumed Thi possibility should be kept n m nd as sour of bias in the i t rp etation of possible effects of these factors

Religion of head of household may have a limited discriminatory function as it is a fairly homogeneous variable most families being orthodox Christians Variations with regard to ethnic group are greater Education of mother is also a homogeneous factor which will have little chance to show its possible associations with childhood acute morbidity Education of father is a variable which displays more variation Fathers on the other hand would traditionally have little direct influence over the care of the children Taking the education of both parents into account a combined education variable may be created in the following way Both parents literate both parents illiterate one parent literate As we can foresee difficulties in the interpretation of a variable of this type we have not included it as a predictor

The creation of attitude and knowledge variables that are uniquely interpretable is not an easy task Due to the uncertain accuracy and validity of the variables Knowledge of vaccination and Cause of measles we have thus chosen not to include them as predictors in the AID runs The traditional health practices may be more accurate as reflections of health attitudes The most universally spread practice is probably uvulectomy (**) which most children undergo early in life The fact that the traditional practices are highly intercorrelated (*) is also a reason for choosing Uvulectomy as the only representative for their group One difficulty is that this variable was registered for individual children As an operation performed in the past cannot be expected to influence acute morbidity as measured at a far later stage this variable will rather be regarded as an indicator of the family s tendency to undertake such operations. Even if it were desirable it is not however possible to create a household index for Uvulectomy as both the number of children and their ages vary between the households As the incidence of uvulectomy increases cumulatively with age about 0 % of children above the age of one year having undergone the operation the effect of this variable may have different interpretation in different age groups

The variable Any vaccination given to child shows little variation most answers being "yes" Furthermore as there are also some difficulties in interpreting this variable we have decided against using it as a predictor Clinic utilization was measured during the same period as acute morbidity and was shown to be partly determined by the acute morbidity It is therefore not logical to use it as an explanatory variable in this study

With regard to the individual variables Age of child must be taken into account as concomitant factor Sex of child would also have to be explored in the same capacity "Weight for age as measured in 1972 is an expression of the nutritional status of the children and may also contribute to the "explanation of variation in acute morbidity Data on parasitic infestations were however obtained in the middle of the longitudinal study Consequently it is not possible to use them with any degree of accuracy as variables since the results could have been very different if the tests had been performed at another stage

Even if some variables have been excluded they may however be introduced in the AID-runs without giving rise to splits (0-ranking) This will provide information about their potential capacity to produce splits and about their relations to the criterion variable in all the splits This procedure will therefore be performed for some of these variables

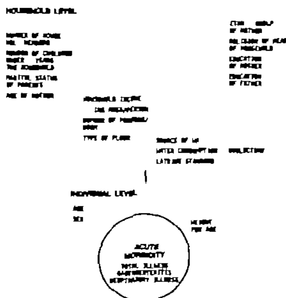


FIGURE 39 A mod l f ac t morbidity with th va iabl sel ted f us in the analy i f v riation

Table A16 lists the variables which we have included as predictors in the AID analyses It also gives the mean morbidity values in the different

sub-classes of these variables thereby illustrating the sources of the variation in this measure of morbidity
effect into account is obvious in the interpretation of several of the variables Thus the higher morbidity noticed in children who belong to households with few members is due to a high proportion of young children in this group whereas the variations are much smaller within the age groups Similar age effects can also be shown in other variables such as Number of children under 5 years and Age of mother

Finally Figure 39 summarizes which explanatory variables are included in the analyses by displaying them in a model of acute morbidity constructed in analogy with the model of child health (Figure 37) Apart from the exogenous variables on the individual level age and sex the distance from the different variables to the criterion variable is intended to illustrate the degree of logical priority in the causal chain

7 4 ANALYSIS OF VARIATION

7 4 1 AID analysis

When considering the model of acute morbidity several strategies are available for the analysis of variation It can thus be performed in stages starting for instance with the clearly exogenous variables followed by the other variables on the household and individual levels in a second or third stage respectively If the pooled residuals were used in the second or third stage this would however limit the possibility of studying the overall interaction effects between the variables This is also more important than achieving the maximum explanation in terms of reduction of variation If the ranking options were used our ability to discover interactions between second and third stage variables with first stage variables would also be limited By using the AID approach in the general screening for powerful predictors and interactions we will therefore introduce the variables simultaneously and consider their level and degree of logical priority in the phase of interpretation and in the construction of causal models

In the first stage we have used the conventional approach in the AID analyses The 19 explanatory variables listed in Table A16 have thus been investigated with regard to their capacity for reducing the variation around the mean morbidity values for Total illness (p_T) Gastroenteritis (p_G) and

Respiratory illness (p_R) weighted by the Number of home visits (see 5 4 4 p 79) The resulting AID-trees' (Figures 40 41 and 42) indicate which variables produce the most homogeneous sub-groups by stepwise dichot omies of the original parent group of 749 children For comparison Tables A17 A18, and A19 list the maximum reduction of the total variation which each predictor can achieve (BSS in % of TSS) in each sub-group In these AID runs a minimum group size of 15 and a BSS which exceeds 0 8% of the TSS have been used as stopping criteria

It is obvious from these analyses that the age factor is the most dominant predictor giving rise to the first splits and in the case of Total illness also to a second generation of dichotomies leaving limited variation for the other variables to explain before the stopping criteria are met As can already be seen in the scattergrams of individual morbidity by age (Figure 6) most of the variation is found in the younger age groups and it is also mainly within these groups that further sub-divisions occur The lack of symmetry in these splits points to the possibility that the variables that produced them or those which are almost as good predictors may interact with the age variable This motivates a closer look at the effect of these vari ables in different age groups

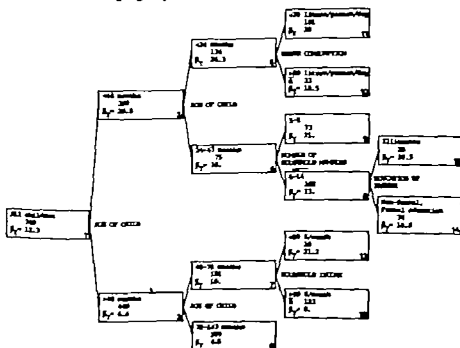


FIGURE 40 AID analy is of variation in Total illnes (p_T) among all children below the ge of 12 years

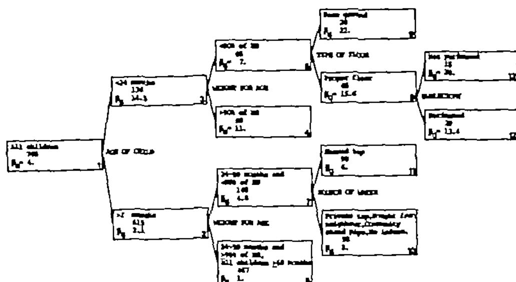


FIGURE 41 AID-analysis f vari tion in Ga troente itis (p_G) among all child en below th ag of 12 years

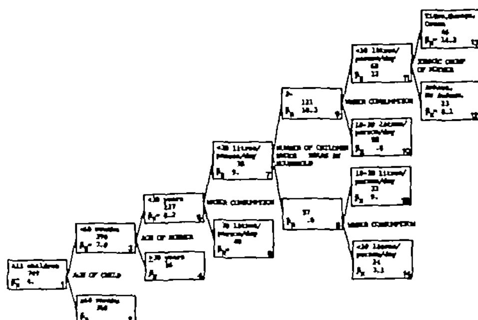


FIGURE 42 AID analy i f i t on i Respirat ry illne s (p_R) among ll hild below the ag f 12 years

Figure 43 displays the morb dity values with regard to Total illness Gastroenteritis and Respiratory illness in children aged 0-23 and 24 59

months divided into different Weight for age -groups The general picture that emerges is that increasing weight for age is associated with decreasing morbidity in both age groups with regard to Total illness and Gastroenteritis In the case of respiratory illness there is no such trend and

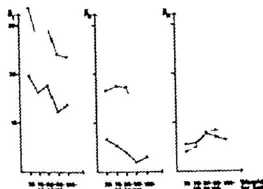


FIGURE 43 Mean morbidity (p n %) by age gr up and w ight f g in % f the Harv d Standa d (T Total illnes G=Gast oenteriti R Re pi r tory illne 0-23mo th ---- 24 59 month Sou ce Tabl A16)

the differences between the age groups are much smaller The Weight for age variable appears early in the AID analysis of Gastroenteritis di viding the age group 0-23 months at the level of 90 % of HS The symmetrical split in the age group 24 143 months is however partly an age effect resulting in a sub-group with high morbidity which consists of children aged 2 4 years weighing less than 90 % of HS and a low morbidity group mainly consisting of all the children over the age of 5 years for which weight information was not collected The latter group however also includes children aged 2 4 years and weighing 90 % of the Harvard Standard or more who have a p_G similar to that of the older children (Table A16) It is therefore reasonable to accept these splits as due to the predictive power of the Weight for age variable A causal interpretation would be that the nutritional status may be an important determinant of the child s load of diarrhoeal disease

Household income is also negatively associated with Total illness and Gastroenteritis (Figure 44) in all age groups This is manifested in the AID analysis of Total illness in the age group 48 71 months from which a small sub-group belonging to the lowest income group and with high morbidity (this is not obvious from Figure 44 which uses another age classification) is split off In the AID analysis of Gastroenteritis household income comes close to Weight for age as a predictor in the age group 0-23 months

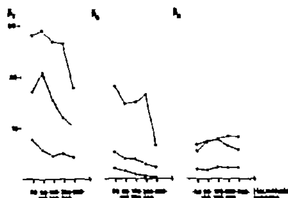


FIGURE 44 Mean morbidity ($\bar{p}$ in %) by ge group and Household income in Eth $ (T Total illness G=Gastro-enteritis R=Respir tory illness = 0-23 months —— 24 59 months —— 60 143 months So rce:Tabl A16)

Figuro 45 shows a similar relationship between Age and Water consumption in the caso of Gastroenteritis The youngest age group seems to benefit most from increased water consumption although this variable does not givo

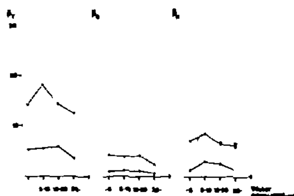


FIGURE 45 Mean morbidity (p in %) by age group and W ter consumption in lit es pe h useh ld member and day (For notations se Fig re 44 Source: Table A16)

rise to any splits A confounding factor is the relatively high $\bar{p}_G$ in the large "No information class which has been attached to the highest consumption groups (Table A16) The corresponding p_R values are low and reinforce the power of Water consumption as a predictor of Respiratory illness Some of the splits caused by the 'Water consumption variable in the AID analysis of Respiratory illness may therefore have occurred by chance especially as no consistent effect of water consumption is indicated in Figure 45 The combined patterns in Gastroenteritis and Respiratory ill ness may have caused the split according to 'Water consumption in the AID analysis of total morbidity

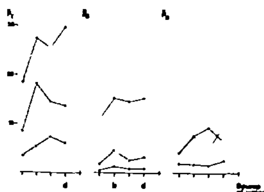


FIGURE 46 Mean morbidity (p in %) by ge group and Sou ce f wat (Privat wat r tap b=Sh red wat r t p Bo ght from neighbo r d Community tand pipe For ther notations see Figur 44 Sou T ble A16)

Source of water gives rise to a split in the AID analysis of Gastroenteritis The general pattern is that children in the households with private water taps have the lowest morbidity (Figure 46) In households which share water taps children in the middle age group have the highest 'Total ill ness and Gastroenteritis rates The explanation for this is unclear but one may speculate as to whether there are differences in the quantity or the quality of the water used or in the way that the water is used within those households A further division according to water consumption makes the interpretation very uncertain as the resulting sub-groups become very small

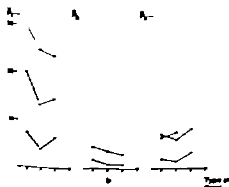


FIGURE 47 Mea morbidity (p i %) by ge group and Type of floor (a=Ear ground b=Wooden floo c=Tiles tone etc Fo the notations see Figure 44 So ce Tabl A16)

The absence of a proper floor seems to be generally associated with high morbidity especially with regard to Gastroenteritis in the youngest age group as suggested by the AID analysis (Figure 47) A natural interpretation is that the younger children are prone to ingest infected material when crawling around on an earthen floor

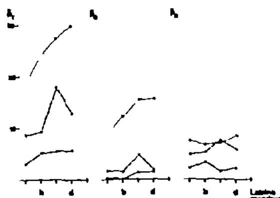


FIGURE 48 Mean morbidity ($\bar{p}$ in %) by age group and Latrine standard (a=Water flush toilet b Private pit latrine c=Shared pit latrine d Public pit latrine For ther notations se Figure 44 Sourc : Table A16)

Latrine standard also appears to interact with age with regard to Total illness and Gastroenteritis rates (Figure 48) This is to some extent supported by the AID analyses where this variable appears to be a fairly good predictor in several sub-groups without however giving rise to splits (Tables A17 A18 and A19)

Finally the Number of household members is also capable of reducing vari ation in morbidity causing one split in the AID analysis of 'Total illness There is no ready explanation for the negative association with morbidity (Table A16) but it could be an age offect as smaller households also had on an average younger children A similar interprotation may hold for the effect of Age of mother and Uvulectomy The number of children under 5 years in the household was thought to influence the chances of children to contracting infectious illnesses This factor seems to operate in the youngest age group especially in the case of Respiratory illness (Figure 42) Education of father has a large No information class which mainly consists of children with single mothers Their high morbidity is apparently responsible for the appearance of this variable in the AID analysis of Total illness (Figure 40) whereas the effect of ethnicity in a small sub-group is more difficult to interpret (Figure 42)

7 4 2 AID regression analysis of morbidity on age

The above analysis has focused on structuring the sample into sub groups (target groups) which with regard to the variation in the dependent vari able are as homogeneous as possible The AID method has served this purpose by splitting the sample by means of a simple one-way analysis of variance technique

From the results it is obvious that age is the overall dominant variable that has to be accounted for before other factors become evident This does not mean of course that they are less important or less relevant in the causal process only that the age effect has to be removed before we can see what else matters

The AID algorithm offers a new feature which was developed to deal with the problem of a dominant explanatory variable (os) Since the original "means analysis" in those cases "consumes" a substantial portion of the sample one can assume a particular relationship between the dependent variable and the covariate and let the chosen function characterize each sub-group rather than the simple mean

Data suggest (Figure 6) that a linear morbidity by age relationship will suffice to remove much of the age effect Technically the total sum of squares in a regression analysis would then at each step of analysis be explained by differences in the two sub-groups regression lines

$$p_i \quad p_i \quad b_i(A \quad \bar{A}_i) \qquad\qquad i \quad 1\ 2$$

where p_i and $\bar{A}_i$ are mean sub-group morbidity and age b_i is the sub-group slope of regression and p_i the estimated sub-group regression line

The overall regression line $p \quad p \quad b(A-\bar{A})$ assuming that all observations come from a single population accounts for the variation

$$\sum_{j\ 1}^{n_c} v_j(p \quad p)^2 \quad b^2 \sum_{j\ 1}^{n_c} v_j(A_j \quad \bar{A})^2$$

where v_j the number of home visits for child no j are the weights employed in the analysis (see section 5 4 4)

$$b^2 \sum_{j\ 1}^{n_c} v_j(A_j \quad \bar{A})^2 \Big/ \sum_{j\ 1}^{n_c} v_j(p_j \quad p)^2$$

is the proportion of the total variation due to the overall linear regression of morbidity on age Thus there remains about the overall regression line the variation

$$\sum_{j=1}^{n_c} v_j(p_j \quad \hat{p})^2 = \sum_{j=1}^{n_c} v_j\{p_j - [p \quad b(A_j - \bar{A})]\}^2$$

to be "explained" by sub-group regressions

The binary split of the total sample is performed so that the variation about the two sub-group regressions (the residual sum of square)

$$\sum_{i=1}^{2} \sum_{j=1}^{n_{ci}} v_j(p_{ij} - p_i) \quad \text{is minimized} \quad (\sum_{i=1}^{2} n_{ci} = n_c)$$

The between-groups regression sum of square criterion will then give

$$BRSS = BSS + \sum_{i=1}^{2} RSS_i \quad RSS$$

where

$$BSS = \sum_{i=1}^{2} \sum_{j=1}^{n_{ci}} v_j(\bar{p}_i \quad p)^2$$ is the sum of square between group means

$$RSS_i \quad b_i^2 \sum_{j=1}^{n_{ci}} (A_{ij} \quad A_i)^2$$ is the sum of square due to regression in group no i i 1 2 and

$$RSS \quad b^2 \sum_{j=1}^{n_c} v_j(A_j \quad A)^2$$ is the sum of square due to overall regression

BRSS is then the gain (reduction in variation) achieved by using two regression lines (means and slopes) instead of one

The dominance of the Age variable in the previous AID analyses is especially pronounced in the case of Total illness and Gastroenteritis The overall individual relationships between age and morbidity are illustrated graphically in Chapter 2 in the form of scattergrams (Figure 6) The regression of morbidity on age verifies the impression that the best linear relationship is found in the case of Total illness (p_T) in the original sample of 749 children Similar results are found in the case of Gastroenteritis (p_G) whereas the regression of the measure of Respiratory illness (p_R) on Age results in a much smaller reduction of variation and a poorer fit of the straight line (Table 9)

Also when limited to the age group 0-59 months a linear regression results in an improved reduction of variation and a better fit in the case of Gastroenteritis The same is true about Respiratory illness where however the total variation is lower and the slope indicates less impressive changes with age

TABLE 9 Regression f p_T p_G and p_R o ag in the original ampl s f children aged 0-143 mo the and child under the ge f 60 month

Age group	Illnes g oup	p p b(A A)	TSS	RSS	$\frac{RSS}{TSS}$	
0 143 mon hs 749	Total Illness	12 27 0 2026(A-58 45)	355 40	83 00	2335	48
	Ga roent Iti	4 27-0 1008(A-58 45)	96 93	20 56	2121	46
	Respiratory Illnes	4 50-0 0662(A-58 45)	82 36	8 85	1075	33
0-59 months 390	T tal Illnes	19 05-0 3531(A 27 75)	210 37	21 16	1006	32
	Gastroente i i	7 40-0 3251(A-27 75)	72 77	17 89	24,8	,4
	Respiratory Illnes	7 62 0 2820(A-27 75)	52 52	13 49	2549	8

The regression of morbidity on age does not however completely exclude effects of the age factor in the AID divisions as the age groups may still be represented differently in the various sub-classes Children in households with few members are thus considerably younger on an average and have a correspondingly higher morbidity than the children in the larger house holds This explains some of the divisions accord ng to umber of household members in the conventional AID analysis (Figure 40) To prevent similar effects we have excluded this variable as a predictor in the AID regressi n analyses Differences in age representation however still occur in some other variables (Table A20) a fact which has to kept in mind during the interpretation

We have chosen to limit the AID-regression analysis to the case of Gastroenteritis in the age group under 5 years The bulk of this illness and its decline with age takes place during this age span The results indicate that Source of water and Water consumption also act as powerful predictors in this analysis (Figure 4 Table A21) Weight for age turns out to have the highest capacity for reducing the variation in the original parent group thus supporting our previous interpretation f the findings in the convent onal AID-ana ysis (Figure 41) The next predictor according to [illegible] (Table A22) is Marital status of parents Children of single mothers have the highest tendency to differ from regression regr ssion f age This vari able is however also correlated Weight for age as its predictive power disappears in the [illegible]

$$\sum_{j=1}^{n_c} v_j(p_j \quad p)^2 \quad \sum_{j\ 1}^{n_c} v_j(p_j \quad [p \quad b(A_j - \bar{A})])^2$$

to be 'explained" by sub-group regressions

The binary split of the total sample is performed so that the variation about the two sub-group regressions (the residual sum of square)

$$\sum_{i=1}^{2} \sum_{j\ 1}^{n_{ci}} v_j(p_{ij} \quad \hat{p}_i)^2 \text{ is minimized} \quad (\sum_{i=1}^{2} n_{ci} = n_c)$$

The between groups regression sum of square criterion will then give

$$BRSS = BSS + \sum_{i\ 1}^{2} RSS_i - RSS$$

where

$$BSS = \sum_{i\ 1}^{2} \sum_{j\ 1}^{n_{ci}} v_j(\bar{p}_i \quad p)^2$$ is the sum of square between group means

$$RSS_i = b_i^2 \sum_{j\ 1}^{n_{ci}} (A_{ij} \quad A_i)^2$$ is the sum of square due to regression in group no i i 1 and

$$RSS \quad b^2 \sum_{j=1}^{n_c} v_j(A_j \quad A)^2$$ is the sum of square due to overall regression

BRSS is then the gain (reduction in variation) achieved by using two regression lines (means and slopes) instead of one

The dominance of the Age variable in the previous AID analyses is especially pronounced in the case of Total illness and Gastroenteritis The overall individual relationships between age and morbidity are illustrated graphically in Chapter 2 in the form of scattergrams (Figure 6) The regression of morbidity on age verifies the impression that the best linear relationship is found in the case of 'Total illness (p_T) in the original sample of 749 children Similar results are found in the case of Gastroenteritis (p_G) whereas the regression of the measure of Respiratory illness (p_R) on Age results in a much smaller reduction of variation and a poorer fit of the straight line (Table 9)

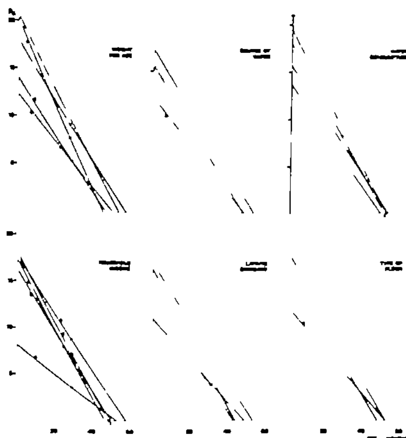


FIGURE 50 AID-regression analysi f mo bidity (Ga troent iti p_G) on ge by vari bl sub-cla se (Source T bl A20)

Variable					
Weight for age	70 % of [illegible]	70 80	80 90	90 [illegible]	[illegible]
Source of water	Privat tap	Shared tap	Bought from neighbour	Community stand pipe	
Water consumption	litres/person/day		20	20	
Household income	50 Ksh. [illegible]/month	50 100	100 300	300 500	500
Type of floor	Bare ground	Wood	Stone tiles cement		
Latrine standard	Pr vat water flush toilet	Pr vate pit latrine	Shared pit latrine	Pub ic pit	[illegible]

ly greater within the lower age ranges than in the older ones whereas the reverse is true about the proportional or relative differences within these age groups It is our opinion that the absolute differences are most relevant especially as the younge ge groups in spite of their size are responsible for the bulk of illness (Figure 4) Thus even if p were to be reduced in the same proportion in the different age groups the quantitative effects would be noticed mainly within the lower age ranges This reasoning is lso applicable to the interaction effects in the conventional AID-analysis (Figures 43-48) although there are some irregularities which may be partly due to group sizes and chance effects caused by the somewhat artificial divisions of the material into three age groups

The dichotomies of the upper branch of the AID tree (Figure 49) indicate possible interaction effects between weight for age Source of water and water consumption Figure 51 shows that particularly low p_G values in the lower age ranges are associated with the combination of normal weight for age and Private water tap in the household whereas malnourished

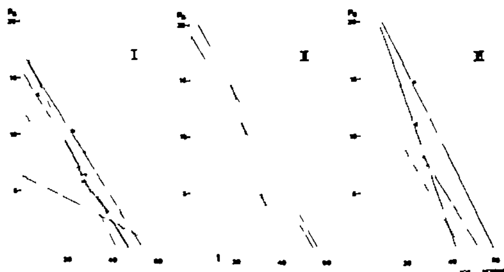


FIGURE 51 AID regression of morbidity (Gastroe teritis p_G) on ag by Weight f r age Source of wat Wat r consumption

Weight of age	Source of water	Water consumption	
[illegible]	Private tap		
	Shared tap		
	Communal stand pipe		
[illegible]	Private tap		
	Shared tap		
	Community stand pipe		
[illegible]	Shared tap	[illegible]	ltrs/person/day
	Shared tap		
	Other sources of water	[illegible]	
	Other sources of wat	[illegible]	
[illegible]	Shared tap		
[illegible]	Shared tap		
[illegible]	Other sources of water		[illegible]
[illegible]	Other sources of water		

children in households with private water taps have the same morbidity due to diarrhoea as children in the other households

According to Figure 51 differences in water consumption plays a minimal role in children who belong to households which share water taps whereas they seem to be of predictive importance for the load of diarrhoeal disease in the other children This is also manifested by an AID division. Figure 51 displays the corresponding analysis of weight for age which has different

effects in sub-divisions according to Source of water but gives rise to an AID split only for children who belong to households which share water taps

7 4 3 THAID analysis

The AID-method analyses variation around mean morbidity values and the AID-regression method variation about linear regressions of morbidity on the age covariate A conceptually different approach in the analysis of differences in morbidity patterns is to regard the criterion variable not as a continuum but as a categorical variable It is for example difficult to claim that a morbidity value of 20% is twice as serious as one of 10% A fruitful approach would thus be to explore what determines low in contrast to high morbidity

As mentioned in Section 7 2 an addition to the conventional AID procedures is the THAID-version which explores differences in the shapes of frequency distributions over sub-classes of the criterion variable in contrast to the use of a summarizing descriptive single measure This approach is also motivated logically as the distribution of p_j is skewed and the mean values are to a large extent influenced by extreme values (Figure 5 p 17) According to the Theta or Delta criteria (p 107) maximal differences in sub-divisions with regard to the various independent variables are then the basis for dichotomous splits of a sub-group

We have chosen to elaborate on the THAID-method more in detail in a separate publication That it is a promising approach is however illustrated in Figure 52 which shows its use in the analysis of Gastroenteritis in the 390 children under the age of 5 years The Delta-criterion is thus maximized (using the same set of independent variables as previously) by a split according to Age under and over 24 months The differences in distribution are as can be seen highly significant Thus 25% of the younger children have a p_G under 5% whereas the corresponding figure among the older children is 76 A further illustration of this method is given in Table A23 where the same set of independent variables has served to discriminate between illness categories Weight for age is thus the strongest predictor for differences in the younger age group while in the older age group Living area maximizes the criterion This is however closely followed by Water consumption and Latrine standard This again emphasizes the impor-

-

tance of the height for age and the hygiene and sanitation variables in the determination of high and low morbidity



FIGURE 52 THAID-analy is f Gastroent riti in children und r 5 yea s (The figure shows only the first dichotomy according to Age)

7 5 REDUCING THE NUMBER OF VARIABLES

Regarding the different AID techniques mainly as instruments for exploring which variables seem to be most important in accounting for variation in the measures of acute morbidity we can use the results of the AID analyses to reduce the number of variables to a reasonable and more practical level This in turn leads to a revision of the original model (Figure 53)

It is interesting to note that most of the variables which can be retained according to this criterion indicate areas which are potentially available for intervention to control morbidity This is true of Water consumption Source of water Latrine standard and Type of floor This may also be claimed about Household income if it is taken to represent the general standard of living Measures of crowding on the other hand appear relatively insignificant as predictors of morbidity A great deal of the variation in morbidity which is due to measures of household composition such as Number of children under 5 years and Age of mother seems to be related

only to the differences in age between the various sub-classes Marital status on the other hand is a more obvious source of variation reflecting the differences in standard between children with single mothers and those in complete families

The high rate of illiteracy limits the possibility for Education of mother to manifest itself as a predictor in the AID analyses A breakdown on sub-classes however reveals differences in morbidity rates especially in the case of gastroenteritis The same is true of Education of father even if this variable presents some interpretation difficulties We suggest that these variables are retained as they have practical and theoretical interest The small number of Muslim children in the material have comparatively low morbidity On the whole however Religion of head of household as well as Ethnic group of mother contribute very little to the variation in morbidity This is also true of Uvulectomy which also displays an inconsistent relationship with the morbidity measures that may be partly explained as an age effect

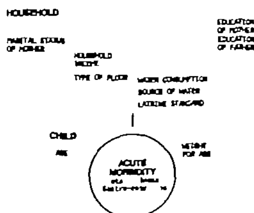


FIGURE 53 A vi d model f cut morb dity wi h i bles whi h appea l va t f th f the naly i f qua titative and causal ff

On the individual level the AID analyses emphasize the major importance of the ge factor but lso draw attention to Weight for age which ndicates that the nutritional status may be an important source of variation in mor

bidity particularly in the case of Total illness and Gastroenteritis It is also with regard to these two measures that interaction effects occur *for instance between age and other independent variables This however* also exposes the limitations of the AID approach and illustrates the necessity for a more detailed consideration of the causal structure that our model represents if we want to use it as a basis for realistic hypotheses about effective measures to promote child health

CHAPTER 8

TOWARDS QUANTITATIVE AND CAUSAL INTERPRETATIONS

8 1 RELATIVE IMPORTANCE BASIC CRITERIA AND A TECHNIQUE

The previous AID analyses have served to locate some variables measured on the household and individual levels which seem important in accounting for the variation in the measures of acute morbidity In addition they have provided us with some knowledge about the patterns of interaction and the shape of the relations between independent and dependent variables

If however we want to use the various measures of statistical association for more constructive purposes than mere prediction they will have to be translated into measures of practical importance which are interpretable and relevant in a health planning situation

When discussing the assessment of the relative importance of variables a problem often encountered in the social sciences Blalock (a) distinguishes between quantitative and causal criteria He points out that although vari ous measures of association can be regarded as quantitati e criteria they can be used in a meaningful way only for the purpose of specific comparisons

> *one would not ask whether temperature is more important than volume in determining the pressure f a gas in an enclosed space But one could assess the change produced in pressure by a given change in either temperature or volume and one might then answer the questions as to which of these specific changes had the greatest effect on pressure The quantitative criterion can be applied only to specific cases and not abstract relationships among the variables*

The second category of criteria involve the causal ordering among the vari ables

> *Briefly put, if A causes B and B in turn causes C it may be argued that A is more important than B in determining C since A is the more ultimate cause, whereas B is merely an immediate cause*

Blalock points out that even if these two criteria may be contradictory in some situations the social scientist cannot ignore the problem or causality as the variables he deals with are linked together in a rather complex causal network and the criteria must reflect this A quantitative technique is needed which can take into consideration the various causal relationships among independent variables Blalock emphasizes that the common tech nique of using a single multiple regression equation does not adequately serve this purpose as it describes the relationship between a dependent and an independent variable with the unrealistic assumption of fixed values for the remaining independent variables The direct as well as the indirect effects of changes in the independent variables could however be described by a series of equations provided that one commits oneself to a specific causal model It would then be possible for the social scientist to ask meaningful questions such as "What is the way to produce a given change in a given variable?"

Path analysis is an analytical tool that permits a causal interpretation of a postulated model It does not purport to demonstrate causality it merely works out the logical and quantitative implications of the model assumptions as depicted by functional relationships between the variables Thus it forces the researcher to be explicit and systematic when postulating his model which will serve as an approximate representation of reality

Path analysis has been used (1 2 3 4 [illegible]) and will be of potential use in the socio-medical sciences and is especially suited for the development of models and the relative evaluation of plausible models in a systems theory approach

Path analysis originates from Wright ([illegible]) and Tukey ([illegible]) and the genetic and biological sciences It is based on the following assumptions

[illegible]ity which means that a variable may not at the same time be cause and effect

additivity interaction effects if present have to be built into the model

linearity each dependent variable is related to its postulated deter minants by multiple linear functions

[illegible] data qualities categorical variables may be incorporated by means of dummy variables ([illegible])

Several authors (75 78 78 80) have studied the effects of departures from these assumptions and suggested ways to get around them.

The estimation procedure in path analysis is similar to that in multiple regression analysis using ordinary least square estimation of linear relationships To ensure comparability the (path) regression coefficients are usually standardized i e the analysis is undertaken on variables scaled to zero means and unit standard deviations The standardized beta coefficients are called path coefficients and measure the expected change in standard units of the dependent variable that results from one standard unit change in a determinant An ordinary regression coefficient however measures the expected difference between two groups that differ by one unit with regard to the determinant Path analysis also permits a more adequate interpretation of the impact of a determinant since it takes into account the operation of indirect and spurious effects

Instead of giving a formal description of path analysis here we will refer to Land (78) for a detailed presentation of the method and concentrate on an illustration of its use with regard to our present problem.

8 2 PATH ANALYTIC SOLUTIONS IN THE CASE OF GASTROENTERITIS

A review of the previous chapters shows that from a quantitative point of view the main morbidity problem is found in the younger age groups Although they constitute only 52 % of the total sample of children under the age of 12 years children under 5 can be estimated as being responsible for 80 % of the total time spent in illness (Figure 4 Table A1) Gastroenteritis in particular dominates in the age group under 2 years but is still responsible for 42 % of the total time spent in illness by the whole group of children under the age of 5 years The various AID analyses have suggested that several of the independent variables are substantial sources of interpretable variation in the measure of gastroenteritis which does not seem to be the case in respiratory illness This reason and the fact that our measure of 'Total illness' lacks specifications with regard to its component of Other illness makes gastroenteritis in the age group 0-5 years a relevant case for quantitative considerations especially as it may also be argued from the clinical point of view that diarrhoeal disease may be particularly detrimental in young children

A path analytic solution will allow us to make estimations about the direct and indirect effects of a certain change in an independent variable in terms of decreased incidence of diarrhoea The prerequisite is however that we postulate a specific causal model

It would obviously be wrong to test a model on the data from which it is generated. We will therefore regard the following path analysis more as an illustrative example than as a confirmatory study

'Weight for age' was measured before the series of morbidity information was collected In this sense it is logically prior to the gastroenteritis variable As it represents a measure of the individual s nutritional status there is also clinical and immunological evidence for regarding it as a close determinant of the occurrence of diarrhoea The synergistic interaction between infection and nutrition however also implies that the nutritional status may be partly determined by previous infection This also means that other factors such as the sanitation and hygiene variables which may be assumed to have a direct influence on the rate of infection may also have this effect via the nutritional status This would be directly determined by the individual s food consumption (for which we have no measure) and this may in turn be related to the economic level of the household It may also be assumed that the economic status will partly determine variables such as 'Water consumption Source of water and Latrine standard

A hypothetical model of this kind can obviously be made very complicated to cover the complex pattern of causation which certainly exists in reality When postulating a causal model (Figure 55) we have however only considered the variables which were discussed in Section 7 5 as substantial sources of variation in morbidity Marital status and Education of mother are clearly exogenous to the other factors on the household level and we have assumed that their effect is mediated via the income variable Age represents a powerful exogenous factor on the individual level

To achieve metric qualities the categorized variables were made into dummy variables using information from Chapter 7 (Table A16 Figures 43-48 and 50) A description of these transformations is given in Table A24 With regard to Water consumption the class mid-point values could have been used but as the relationship between this variable and morbidity seems to be non-linear we have chosen to use it as a dummy variable with a dividing level at 20 l/person/day according to the empirical pattern (Figure 45) No

information is available in medical literature about what constitutes a critical public health level of Water consumption (148)

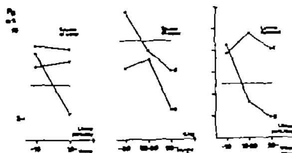


FIGURE 54 Basis f the interactio variables used in the p th analysis f morbidity due t Gastroenteritis (p_G) (Sha ed w t r tap b = Community tand pipe c Privat w t tap d = Shar d wat tap = Other sourc f wat r than shared tap f = Privat latrine g No p ivate latrine) The broken lines indicat the divi ions made to create dummy variables

The previous AID analyses and the AID regression analyses point to the ex istence of moderate interaction effects between Age and several other in dependent variables Several of these are however due to deviating mor- bidity values in small extreme groups e g in the case of Household income and Latrine standard The AID analyses indicated the existence of inter action effects also between variables measuring hygiene water consumption and nutrition Further analysis of the whole group of children under the age of 5 years indicates that the most pronounced interaction effects are those described in Figure 54 These were used as the basis for the creation of 3 additional dummy variables (Figure 55 variables SN LW and SW)

The difficulty of ascribing specific values to the No information classes creates a problem with regard to the variables 'Household income Water consumption and 'Weight for age We have therefore chosen to limit the path analysis to 280 of the original 390 children under 5 years

Figure 55 displays in a path diagram the postulated causal relationship (one way arrows) between variables in a multivariate system determining morbidity in gastroenteritis It is of course an oversimplified model in

the senso that it considors only a limited number of variables with low metric qualities This model can also be described by a set of structural oquations representing the causal process These lead to simple parameter estimation procedures in the case of recursive models Variations in and correlations between the exogeneous (ultimate) variables (M E_m E_f A) are assumed to be caused by variables outside the system The total variation of each endogeneous (dependent) variable is assumed to be completely deter mined by the system Unmeasured variables are accounted for by residual variables assumed to be mutually uncorrelated and uncorrelated with other determinants in the system

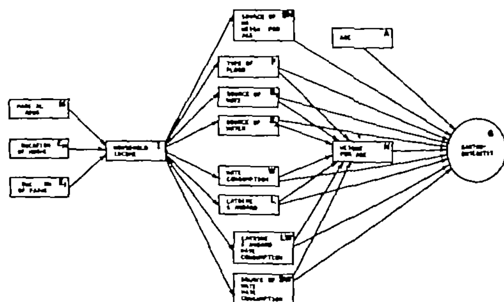


FIGURE 55 Path di gram postulat d for the nalysis of morbidity due to gast oent itis

Thus

$$G \quad P_{GA}A \quad P_{G\,SN}SN \quad P_{GF}F \quad P_{G\,S_1}S_1 \quad P_{G\,S_2}S_2 + P_{GW}W + P_{GL}L \quad P_{G\,LW}LW$$
$$P_{G\,SW}SW \quad P_{GN}N \qquad (8\ 2\ 1)$$

is the estimated relationship between gastroenteritis and its postulated determinants A S F S_1 S_2 W L LW SW and N expressed in standardi ed form P_{GN} is the path coefficient expressing the direct effect of nutri tional status on gastroenteritis measuring the fraction of the standard deviation of G for which N is directly responsible

The values of the path coefficients produced in a first analysis were used to identify the most important variables Thus when a path coefficient did not exceed twice its standard error the respective independent variable was considered to have no effect on the dependent variable and the path was excluded from the diagram This enabled us to reduce the complexity of the path diagram, retaining only the most important variables The revised path diagram is displayed in Figure 56 Both variables expressing Source of water have thus been excluded as well as one of the interaction variables and Latrine standard The latter variable is highly correlated to gastroenteritis morbidity but this may be partly explained by the fact that it is also highly correlated to Type of floor (see correlation matrix Table 10) The interaction between Latrine standard and Water consumption will however still be expressed by the interaction variable LW

TABLE 10 Int rc rr lation mat ix (zero-o de correlations) between variables in th riginally postul ted path diagram (Figure 55)

CODE	VARIABLE	M	E_m	E_f	I	F	S_1	S_2	W	L	N	A	G	SN	SW	LW
M	MARITAL STATUS	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
E_m	EDUCATION OF MOTHER		[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
E_f	EDUCATION OF FATHER			[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
I	HOUSEHOLD INCOME				[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
F	TYPE OF FLOOR					[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
S_1	SOURCE OF WATER						[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	
S_2	SOURCE OF WATER							[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
W	WATER CONSUMPTION								[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
L	LATRINE STANDARD									[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
N	WEIGHT FOR AGE										[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
A	AGE											[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
G	MORBIDITY IN GASTROENTERITIS												[illegible]	[illegible]	[illegible]	[illegible]
SN	SOURCE OF WATER WEIGHT FOR AGE													[illegible]	[illegible]	[illegible]
SW	SOURCE OF WATER WATER CONSUMPTION														[illegible]	[illegible]
LW	LATRINE STANDARD WATER CONSUMPTION															[illegible]

A repeated analysis was then made according to a new set of estimated relations

$I \quad P_{IM}M \quad P_{IE_m}E_m \quad P_{IE_f}E_f$

$SN \quad P_{SN\,I}I$

$F \quad P_{FI}I$

$W \quad P_{WI}I$ (8 2 2)

$LW \quad P_{LW\,I}I$

$N \quad P_{NA}A \quad P_{NI}I \quad P_{NW}W$

$G \quad P_{GA}A \quad P_{G\,SN}SN \quad P_{GF}F \quad P_{GN}N \quad P_{G\,LW}LW$

the sense that it considers only a limited number of variables with low metric qualities This model can also be described by a set of structural equations representing the causal process These lead to simple parameter estimation procedures in the case of recursive models Variations in and correlations between the exogeneous (ultimate) variables (M E_m E_f A) are assumed to be caused by variables outside the system The total variation of each endogeneous (dependent) variable is assumed to be completely deter mined by the system. Unmeasured variables are accounted for by residual variables assumed to be mutually uncorrelated and uncorrelated with other determinants in the system

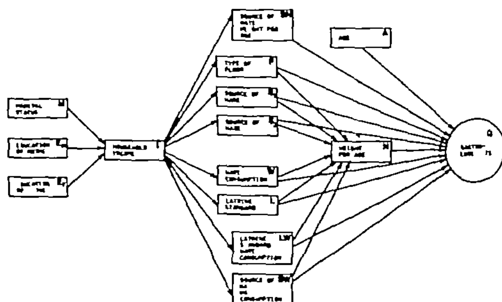


FIGURE 55 Path diagram postulated for th analysis f morbidity due t gastroent ritis

Thus

$$G \quad P_{GA}A \quad P_{G\,SN}SN \quad P_{GF}F \quad P_{G\,S_1}S_1 \quad P_{G\,S_2}S_2 \quad P_{GW}W \quad P_{GL}L \quad P_{G\,LW}LW \quad P_{G\,SW}SW \quad P_{GN}N \qquad (8\ 2\ 1)$$

is the estimated relationship between gastroenteritis and its postulated determinants A SN F S_1 S_2 W L LW SW and N expressed in standardi ed f rm. P_{GN} is the path coefficient expressing the direct effect of nutri tional tatus on gastroenteritis measuring the fraction of the standard de i tion of G for which N is directly responsible

ficient can be given a causal interpretation The remaining components represent indirect causal effects where the effect of an independent variable is mediated via an intervening variable and spurious effects which are due to joint effects of common causes or the correlation between predetermined variables Thus r_{GA} in (8 2 3) is the correlation coefficient between A and G where p_{GA} represents the direct causal effect of A on G and where the remaining terms represent indirect or spurious effect with r_{AN} obviously containing a path coefficient indicating a direct effect of A on N. Since there is a postulated causal relationship between A and N r_{AN} can be further sub-divided in its components as follows

$$r_{AN} \quad p_{NA} \quad p_{NI}r_{AI} + p_{NW}r_{AW}$$

If r_{AN} in this form is re-instated in the original expression we get

$$r_{GA} = p_{GA} \quad p_{G\ SN}r_{A\ SN} + p_{GF}r_{AF} \quad p_{GN}p_{NA} \quad p_{GN}p_{NI}r_{AI} \quad p_{GN}p_{NW}r_{AW} \quad p_{G\ LW}r_{A\ LW}$$

5075 −	5116	0065	− 0075	+ 0179	− 0004	− 0009	− 0093
	direct	purioo	spurious	indirect	spurious	spurious	spurious

Interpretations of the different terms are given underneath the expression $p_{GN}p_{NA}$ is the indirect causal effect from A on G via N. $p_{GN}p_{NI}r_{AI}$ is the spurious part of r_{GA} which is mediated by I via N and $p_{GN}p_{NW}r_{AW}$ is the spurious part of r_{GA} which is mediated by W via N

TABLE 11 Divi ions f th t tal association betwee thre dependent variabl and set f independent variables i the path model of gastroenteriti i children aged < 5 years (vi Wate onsumption ** via Weight f ag)

Dependent variable	Independent variable		Correlation coefficient total	Decomposition direct	Total effect indirect	Spurious
	Marital status	[illegible]	[illegible]	[illegible]		[illegible]
[illegible]	Education of mother		[illegible]	[illegible]		[illegible]
	Education of father	[illegible]	[illegible]	[illegible]		[illegible]
	Age	[illegible]	[illegible]	[illegible]		[illegible]
[illegible]	[illegible]		[illegible]	[illegible]	[illegible]	[illegible]
	Water consumption	[illegible]	[illegible]	[illegible]		[illegible]
	Age	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	[illegible]	[illegible]	[illegible]	[illegible]		[illegible]
[illegible]	Type of floor	[illegible]	[illegible]	[illegible]		[illegible]
	[illegible]	[illegible]	[illegible]	[illegible]		[illegible]
	Latrine [illegible] water consumption	[illegible]	[illegible]	[illegible]		[illegible]

In this way it is possible to determine the components in the associations between dependent and independent variables This is summarized in Table 11 It should be noticed that when G is the dependent variable the correlations do not precisely equal the sums of the direct indirect and spurious effects This has only minor numerical importance and is due to the fact that the relationships involving G have been weighted by the number of home visits whereas this is not the case for the other relationships

8 3 THE PATH MODEL AND A QUANTIFICATION OF COST EFFECTIVENESS A HYPOTHETICAL EXAMPLE

We have now reached the stage when we can use the path diagram for quantitative calculations of the effects of changes in various variables We intend to use the non-standardized path regression coefficients as these are immediately interpretable in the units of measurement The path regression coefficients are found in the path diagram (Figure 56) and the following example will illustrate their use

Let us assume that we can achieve a maximal change for the better in the variables M, E_m and E_f i e there will be no single mothers and all parents will have formal education What would then be the effect on the morbidity due to gastroenteritis provided the relations assumed in our model are realistic?

The effect on income would be

(1-0 354) 1 6 6 (1-0 161) 102 4 (0 089) (41 07) 203 71 $

a raise in mean income to 419 34 Eth $
This in turn would

increase	Ua	with 0 161	units	i e	to 0 265
	W	0 048			0 202
		1 751	"	"	88 88
decrease	F "	0 196	"	"	0 115
	SS	0 0 5	"	"	0 150

which in turn would

decrease G with 0 42 via LW
" 0 02 W and V
" 0 13 " N
" " 0 32 P and
0 24 " SN

The total effect on G from a change (max) in V E_m and E_f = 1 13 i e from 8 09 to 6 96 %

Similarly if all households were to be raised to the highest income class (presumed to have a mean income of 750 Eth $/month) the effect on G would be (750- 15 625)[(0003697) 3 275 + (0009607) 1 6345 008594 (0752) 0002375 5 67(075) 000 89 (6010)] 2 9 30 i e G would decrease from 8 092 to 5 119 As the relationsh ps are assumed to be linear and additive the effects would add up as depi ted in Figure 57 the largest effect being mediated by the interaction f a raise in Latrine standard and Water consumption



FIGURE 57 Hypothetical effect f raise i income from mean l vel f 215 Eth $ to 750 $ (F bbreviations as Figure 56

We may also ask about the quant tati e implicat ons of maximal changes in variables which acc rding to our model assumptions re causally directly rel ted to gastroenterit

Thus

the provision of private latrines to all households and the increase of water consumption by 10 litres/ person/day	would change G by (1 104)(2 6010)=-2 3305
making all children well nourished	would change G by (100-87 129)(0752)=-0 9679
if all houses had proper floors this	would change G by (- 311) 1 6343 - 5083
and if the combination Shared tap and mal nutrition disappeared this	would change G by (225) 3 275 7.62

The total effect on G would be a reduction of 4 53 These effects are assumed to be linear and additive as displayed in Figure 58

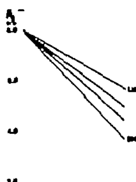


FIGURE 58 Hypothetic l effects f maximal hange in ri bles usally di- tly lated to the inci denc of ga tros t itis

Let us now instead define a desired effect We may for instance want to reduce the rate of gastroenteritis by 25 % This corresponds to 2 025 absolute percentage units in G or 7 3 of 29 2 diarrhoeal days per year and child

One possible question could be what single theoretically possible action would be needed to achieve this? Obviously only a change in LH would suffice Its value would have to increase to 0 8818 meaning that another 77 8 % of the children would have to live in households with private latrines and with water consumption of at least 10 litres per person and day

The necessary change in income would be 363 62 $ while no single action with regard to the education variables would be sufficient to achieve a 25 % reduction in the incidence of gastroenteritis

These examples may suffice to illustrate the quantitative implications of the assumptions made in the postulated causal model A realistic path model would also serve as a tool for the health planner in comparing alternative intervention programs in terms of effectiveness as well as efficiency (cost benefit) if combined with the cost functions of various programs

Well aware of the limitations of our data we have considered some examples of possible programs aiming at the reduction of the load of diarrhoeal disease These examples are summarized in Table 12 We have also considered some hypothetical relative costs attached to each type of intervention to make an exemplification of a cost benefit analysis possible

Hypothetical programs

I The provision of pri ate l t ine for all households lacking this facility and the construction f umbe f wate tand pipes to make wate ea lly acce ibl to all Wat is di t ib ted free of cha ge to inc ease wat consumption by 10 l/day/pe son

II The provi ion of pri ate wate taps and the distribution of wate free of cha ge to ensure that the ave age wate consumption i rease by 10 l/day/person

III Ba ic quality housing to all needy households (g those who live i hous s with no prope floo) i troduction of p ivat lat ines (ll households

IV Food supplement tion to aise weight for g to a normal l vel

V The i troduction of chool sy tems to cove both dult and child en with ba ic formal schooling

TABLE 12 A hypoth tical example of effectiveness and cost benefit calcul tions based on th path analytic model of Gastroent ritis (Programs and r lative costs - in MU monetary units - are hypoth ti al whereas other data re derived from the path analysis For variable not tions s e Table 9)

PROGRAM	[illegible]	Proportion of children to be covered	Cost per child	Mean change	variable	[illegible]	% [illegible] decrease in [illegible]	Cost per % decrease in [illegible]
Private latrines to households		772	[illegible]	LW	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]		[illegible]	[illegible]		
Water taps [illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]		[illegible]	[illegible]	LW	[illegible]	[illegible]		
[illegible] housing	[illegible]	[illegible]	6.12		[illegible]	[illegible]	[illegible]	[illegible]
Private [illegible]		772	[illegible]	LW	[illegible]	[illegible]		
Food supplementation to [illegible] malnutrition	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible] schools for [illegible] children and [illegible] adults	[illegible]	[illegible]	[illegible]		[illegible]		[illegible]	[illegible]

Table 1 summari.es the rolativo costs which we have assumed for each child (calculated in MU monetary units) Lot us for instance consider program I If all households lacking privato latrines were to be given this facility and this were combined with a riso in water consumption by at least 10 litres a day the value of the interaction variablo LW would increase from 104 to 1 00 This increase in water consumption however also implies that the variable W would be changed by 3068 (the proportion of chil dren living in households with a water consumption of 10-20 l/person/day) The same effect would have to be considered when projecting the total effects of program II A similar calculation is also the basis for estimating the change in variable SN (program III) which is due to a riso in the nutri tional level

The effectiveness of program I is highest and when the cost functions are applied it also turns out to have the highest efficiency in terms of decrease in G per MU spent or in terms of cost per unit of decrease in diarrhoe It should be observed however that intervention programs to affect factors which are more indirectly related to gastroenteritis changing for instance factors like education would convey a number of other benefits than the reduction of illness although their effects ould come rather slowly \ ording to the model incom would go up and an increased number

of households would be provided with latrines water etc without any program costs A comprehensive calculation of the costs and benefits should also consider the total social costs of disease which we have not attempted to do here

The main idea behind giving these examples is however to demonstrate the feasibility of path analysis for cost effectiveness-calculations which could then serve as a basis for further economic considerations in health planning There is a special need for the development of imple methodologies in health economics in developing countries (1m) The construction of nomograms which can be used without complicated computational facilities has fo instance recently been suggested to determine the 'cost-benefit balance point" in sanitation-programs in developing countries (11)

If our finding for instance of a strong direct path from the interaction between Latrine standard and Water consumption could be confirmed n the local community as well as in other urban communities in developing countries health programs aiming at the provision of both latrines and water should definitely be considered in cost-effecti eness calculations

The approach that we have demonstrated here can serve as a method of raising the estimation of effectiveness of various intervention programs above the level of pure guesswork and to make cost-effectiveness prognoses more realistic

TABLE 12 A hypothetical example of effectivenes and cost benefit calculations based on the path analytic model of Gastroenteritis (Programs and relative costs - in MU monetary units - ar hypothetical wher as other data a e derived from the path analysis For variable notations see Table 9)

[illegible]	[illegible]	Proportion of [illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]		[illegible]	[illegible]	[illegible]	33	.27	[illegible]
[illegible]	6	[illegible]	[illegible]	[illegible]	[illegible]		
[illegible]	13	[illegible]	[illegible]	[illegible]	73	[illegible]	[illegible]
[illegible]		[illegible]	[illegible]	[illegible]	[illegible]		
[illegible]	39	3	33	33	1	13	[illegible]
[illegible]		778	[illegible]	[illegible]	[illegible]		
[illegible]	13	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	30	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

Table 1 summari.es the relative costs which we have assumed for each child (calculated in MU monetary units) Let us for instance consider program I If all households lacking private latrines were to be given this facility and this were combined with a rise in water consumption by at least 10 litres a day the value of the interaction variable LW would increase from 104 to 1 00 This increase in water consumption however also implies that the variable W would be changed by 3068 (the proportion of chil dren living in households with a water consumption of 10- 0 l/person/day) The same effect would have to be considered when projecting the total effects of program II A similar calculation is also the basis for estimating the change in variable S (program III) which is due to a rise in the nutri tional level

The effectiveness of program I is highest and when the cost functions are applied it also turns out to have the highest efficiency in terms of de- crease in G per MU spent or in terms of cost per unit of decrease in diar rhoea It should be observed however that intervention programs to affect factors which are more indirectly related to gastroenteritis han.ing for instance factors like education would convey a number of other benefits than the reduction of illne s although their effects would come rather slowl A ding to the model income would go up and an increased number

In order to evaluate the morbidity measure used in this study and the design used to generate it we have initially (Chapter 3) assumed a model for the underlying pattern of illness occurrence which we regard as a stochastic process over time made up of illness episodes that may be described according to their frequency and duration We thus consider illness occurrence as a renewal process the character of which we have searched by postulating models of illness susceptibility and recovery propensity An evaluation of these models and an estimation of their parameters was attempted in a supplementary study (Chapter 4) These empirical data do not contradict the validity of the two-state alternating Poisson process as a model of illness occurrence (Figures 8 10 12 13) This means that we assume that both the duration of illness and health episodes follow single exponential distributions i e that a constant recovery propensity throughout an episode is valid We consider these assumptions as realistic at least within fairly homogeneous age and morbidity groups Although one may well speculate about complex models that permit more sensitive analysis accounting for the structure of a material we do not consider it worthwhile to make any further elaboration on the discussion in Chapter 4

The alternating Poisson process has served as the statistical tool in evaluating our illness load measure (Chapter 5) We have shown that its statistical precision (Figures 23-29) is a function of the underlying pattern of illness occurrence i e of the individual s susceptibility to illness and recovery propensity as well as of the study design the interval between home-visits the length of the study and the sample size of children. By means of the model we have evaluated the theoretical implications and studied the relative merits of various changes in survey design

The conclusions arrived at indicat that little advantage (Figures 4 .5) is gained by increasing the intensity in home-visiting above that of fort nightly visits especially in view of the possibil ty that bias due to less acceptance by the community may be a s de effect For more precise statements it is also important to gathe some prior knowledge about the expected episode duration.

In view of the possible presence of seasonal variations (Figure 31) one should aim at a one-year study With regard to statistical precision and in view of limited resources it would be just fied to increase the length of the study rather than the home-visiting intensity (Figure 27) The effects of lengthening the survey should also of course be considered taking into account

illness episode charactoristics (Figuro 26) It would for example suffice to estimate the expected episode duration for each sub-classification of illness and age group The statistical precision could then be assessed as a function of the individual s susceptibility to illness or his true illness proportion

In a longitudinal study one can soldom avoid drop-outs In order to account for the effect on precision of the varying number of home-visits performed (Figuro 28) a weighing procedure is motivated There is however no unique solution to this problem, since the weight function should be assessed by reference to illness characteristics seasonal variations and if possible also to the actual cause for drop-out from the study One should for example guard against the tendency for drop-out to be correlated to some of the important variables under study

The identification and analysis of administrative and statistical design problems were also intended to result in some recommendation for future use in similar studies In undertaking longitudinal community studies of morbidity which are expensive in terms of staff and economy as well as time consuming one may often have to abstain from the theoretically perfect designs for practical as well as economical reasons In this situation it is important to have the instruments that make possible a rational choice of design to achieve optimal information reducing possible sources of errors and non natural variation to an acceptable level

Thus in communities where the sampling of individual children may not be possible it should be observed that the sampling of households or families may induce correlations between children in the same households Control for interviewer or observer bias should be built into the study design The level of drop-out rates should be foreseen and possibly balanced by recruitments of suitable matches

The recall of morbidity experience is a convenient procedure but should not be used as the single source of continuous information since it causes considerable inaccuracy with regard to the specification of both the time and the duration of illnesses If however the number of illness episodes could be accurately recalled by the mothers during for example fortnightly intervals the combination of this information with the fortnightly observation would greatly increase the possibility of forming an accurate measure of the time spent in illness Usin the model of illness occurr nce suggested in

Chapter 5 it would then be possible to estimate its parameters which means that information about the rate of illness occurrence as well as about epi sode duration would be gained We therefore suggest that the feasibility of a combined observation-recall procedure should be tested in practical field work.

• Morbidity patterns

The basic measures of acute morbidity (Figures 2-6) and the distributions of illness frequency and duration (Chapter 4) confirmed the general pattern of childhood morbidity reported from other developing countries (Table 7) where in comparison with figures from industrialized countries the incidence of diarrhoeal disease is particularly high

The mere quantitative domination of acute illness in the younger age groups for instance particularly in children under 2 years of age identifies these as target groups for preventive and curative health programs According to the one-year study children under the age of 2 years could on the average be estimated to have some kind of illness symptoms during 104 days per year out of which 59 days were due to gastroenteritis This illness category also showed the most pronounced age differences Children over the age of 5 years were for example estimated to have diarrhoea only during 4 days per year Although the children under the age of 2 years constituted only 18 % of the total sample of children they were responsible for 50 % of the total time spent with diarrhoea by all children (Figure 4) The age differences were less marked in the cases of respiratory illness and the unspecific group of other illness Even if this study did not collect specific clinical or etiological data it is obvious that the bulk of these acute illnesses are not preventable by the traditional vaccination programs directed against a handful of specific infections and that action has to be oriented against more fundamental causes

In accordance with other reports (ee, ee ee) this study also indicates that malnutrition is associated with an increase in both frequency and duration of gastroenteritis (Table 6) This illustrates the clinically well known synergism between infection and nutrition (ee ee) which is also being increas ingly documented by immunological research (ee) The nutritional status in association with the immunocompetence of the individual is thus one circum- stance which may explain vari tions in illness frequency and duration

Another factor which has implications for the immunocompetence is the pattern of breast feeding which is also being documented as an important determinant of health during the first years of life The present study did not collect any longitudinal data on breast feeding but some figures obtained during the baseline survey and another recent local survey indicate that there is large variation in the breast feeding pattern some children being completely weaned during the first 1/2 year of life whereas other children are still partially breast fed during the third year of life (44) which may explain some of the observed variations in morbidity pattern

These variations may also be related to etiologic differences which were not investigated in this study Outbreaks of diarrhoeal and respiratory illnesses among siblings were usually initiated by children under the age of two years indicating that they were the main introducers of infection in the households The low rate of simultaneously occurring infection among siblings speaks against epidemic spread of food and water borne disease and favours the idea of contact spread which may be determined by the hygienic and sanitary conditions in the households

• Causal interpretations and implications

This study is part of a project which was basically devoted to more general questions concerning the causal structure of child health Consequently attention should be paid to the conceptual framework and logic of the whole research process as well as to the basic ideas and values which directed the investigation

The organization of the study was based on an interdisciplinary collaboration between several local institutions and was characterized by an exploratory approach and a readiness to search for causes of child health problems to identify ways to promote child health in the context of society and socio-environment This approach implies that if important causal factors for child health were to be found in the socio-environment this could lead to a situation where a medical person should advocate social and environmental changes or the building up of community services rather than the extension of traditional medical services In the prolongation the values implicit in a study of this kind will thus clearly by political (85) Regardless of the political system however a health planner in a developing country will have to operate within the constraint of very limited budgets In this situation the need for quantitative data is felt and studies of the present

type may serve a useful purpose

We have attempted to view child health basically from a social systems point of view where the variables may be identified and measured on the society community levels as well as on the household and individual levels Although the Kirkos study deals mainly with variables on the latter two levels we thus want to indicate by the brief discussion on models of health (Chapter 6) that action to promote child health can be taken on all these levels This implies that basic assumptions about the causal order is a pre-requisite for meaningful interpretation. During the course of a 4 year collaborative study it is natural that the initial views and values of the authors that guided the primary evaluation and analysis of data are not identical with those now prevailing Thus we have gradually departed from a positivistic view on the generation of knowledge and are convinced that also in inductive exploratory studies the generation of knowledge should be viewed as a continuous modification of a priori views in the light of empirical data a process which is facilitated by the open and explicit identification of primary knowledge and theory in the actual research field

The AID (Section 7 4 1) the AID-regression (Section 7 4 2) and the THAID methods (Section 7 4 3) served as useful instruments for a basic analysis of variation in the morbidity measures also demonstrating the predictive power and the interactions between the explanatory variables (Chapter 7) On the individual level the child s nutritional status measured as Weight for age appeared as a factor strongly associated with diarrhoeal disease As the measures of children s weight used in this study were obtained before the series of morbidity measures Weight for age represents a factor which is logically prior to morbidity in this analysis The mutual synergistic effects between morbidity and nutrition will however be further elucidated in a separate analysis of longitudinal weight and morbidity data which may give some indications f how this relationship develops over time

Other results of the analysi of ariation illustrate that variables expres ing sanitat on hygiene and housing standard are more powerful as predictors of morbidity than the cultural and demographic characteristics of the household

Statistical measures of the relative importance of various factors for morbidity are however irrelevant unless they can be given a quantitative interpretation A health planne may find it useful to be able to estimate

effect on morbidity of various social and environmental changes but does not benefit from the knowledge that a certain factor is important in an abstract sense We have chosen gastroenteritis in children under the age of 5 years as the criterion variable in a postulated causal model to investigate the feasibility of arriving at quantitative estimations by means of path analysis (Chapter 8) It should be pointed out that this was not done to test the model on the very data from which it was generated The question whether a model includes relevant variables or whether they represent other variables which were not measured can ultimately only be answered by the results of practical programs to promote child health Nevertheless it is interesting to note that if the causal assumptions in the model are realistic the empirical data imply that nutrition and factors in the field of hygiene and sanitation demonstrated for example by the interaction between Water consumption and Latrine standard have definite quantitative implications of profound relevance in health planning situations

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APPENDIX

LIST OF TABLES

TABLE A1 AVERAGE MORBIDITY ($\bar{p}$) BY ILLNESS CATEGORY AND AGE
(n = number of illness observations T = Total illn ss G = Gastroe teritis
R = Respiratory illne s O Other illne s)

Age	No. of children	No. of [illegible]	p_T				p_T	p_G		p_R	Age	No. of [illegible]	No. of [illegible]	p_T				p_G			p_O
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
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[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]		[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]			[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

TABLE A2 INDIVIDUAL MORBIDITY (p_i) BY ILLNESS CATEGORY AND AGE
(bsol te and umulativ percentage distribution f the number of child en)

Morbidity	Age	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Total illness	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Gastroenteritis	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Respiratory illness	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

TABLE A3 Obs rved distribution f the NUMBER OF ILLNESS EPISODES DURING 60 DAYS OF OBSERVATION (1 t row) by illness category and age (T Tot l illness G Gastroent ritis R Re pi t ry illne O = Other illne) compa ed with the fit f a ingl Poisson di tributio (2nd row) and a ompound Poi so di t ibution (3rd row) according t the χ^2-stati ti (χ^2_p and χ^2_C respectively)

TABLE A4 Adjusted observed distributions of EPISODE DURATION in days and ESTIMATED NUMBER OF EPISODES PER YEAR by illness category and age (T Total illness G Gastroenteritis R = Respiratory illness O = Other illness For other notations see text of Chapter)

[illegible]

TABLE A5 Adj t d b rv d di t bu i f INTERVAL D RATIO BETWEEN EPISODES f t t l llne (d y)

[illegible]

TABLE A6 Adjusted observed di tribution of GASTROENTERITIS EPISODE DURATIONS in ge group 0-11 and 12 23 months

d	0-11 months	12-23 months	0-23 months
0-1	0121	1216	1275
1 2	1058	0958	[illegible]
2-3	1453	10 1	1263
3-4	[illegible]	0735	[illegible]
4-5	1124	0733	0947
5-6	1205	0531	0936
6-7	0958	0729	0836
7-8	0636	0464	0567
8-9	0478	0462	0475
9-10	0704	0462	0533
10-12	0708	0306	0466
12-15	[illegible]	0307	0304
15-20	[illegible]	0407	01 1
20-30	[illegible]	1383	0436
30-40			[illegible]
40-50	0310	0704	062
50-60	1		33
Σ	1 000	1 0004	1 0002
s	22	20	42
n_I	1	25	55
d̄	7 2435	2 7406	9 0054

TABLE A7 Adjusted OBSERVED cumulative distributions f 147 GASTRO-ENTERITIS EPISODE DURATIONS among 216 children aged 0-12 yea s compa ed with three FITTED exponential di t ibution

D t	Observ ed	Sing exp	Appro mixed exp	Convolved exp
2	39	2306	2521	2630
4	4624	468	4363	4497
6	5347	5446	57 9	5836
8	7109	6494	6726	6807
10	7696	7304	7575	75 9
15	80 5	[illegible]	865	8605
20	9 03	9273	8852	9 70
30	9754	9804	9746	9644
40	9757	8947	9904	9857
50	9878	9946	996	9937
60	[illegible]	9979	9993	9972
t̄	7 61	7 61	(7 1[illegible] 2 76 6 90 36)	(5 95 7 44

Single exp: F( ) = exp(0 3)

Approx mixed exp: F( ) /147(3 exp -0 30 33 exp -0 0705 +45 exp 0 449 26 exp 303[illegible]

Convolved mixed exp: ( ) 6492 l-exp(0 1964) 0 3508 l-exp(-0 0804)

TABLE A8 Adjusted observed distributions of EPISODE DURATION IN THREE GROUPS OF OTHER ILLNESS"

[illegible]	Sk[illegible] disease	Eye disease	Unspecified other illness
0-	0734	1293	0558
2	038	1153	0536
2 3	030	966	0509
3 4	0641	1037	56
4-5	0446	048	0496
5-6	0617	0587	0455
6-7	0354	0554	0533
7 8	0477	0456	0585
8-9	[illegible]	0240	0 76
9-10	[illegible]	0299	0 55
10- 2	0469	0775	0387
12 5	0555	0267	0402
5-20	346	[illegible]	0342
20-30	2138	0324	0438
30-40	[illegible]	0037	0052
40-50	[illegible]	005	.0040
50-60	734	1444	0474
Σ	[illegible]	1 0000	1 0000
[illegible]	2 6	216	2 6
[illegible]	34	72	73
[illegible]	2 5285	6 0423	8 56 9

TABLE A9 DECOMPOSITION OF THE ESTIMATED VARIANCE OF GROUP MORBIDITY $\bar{p}$ (T tal illnes) pe year (L 364) as functions f the intensity of home-vi iting (L) V_B and V_W denot the estimated variations between and within children

Age i months			0 23	24-59	60-143
Supplementary udy			42	65	109
	V_B		0588	0896	1186
	n		100	186	286
	p		2469	1427	0505
	V_B 0^5		20 38	8 14	3 10
One-year udy		L 28	17 24	8 63	3.36
		L 4	10 87	5 86	2 39
	V 10^5	L 7	8 96	5 84	2 11
		L 4	8 31	4 73	2 05
		L 2	8 23	4 67	2 02
		L	8 0	4 65	2 01
		L 28	37 6	6 77	6 54
		L 4	3 24	4 60	5 57
	V( ) 10^5	L 7	29 34	3 8	5 29
		L 4	28 69	12 07	5.22
		L 2	28 58	12 40	5.20
		L	28 56	2 79	5 9

TABLE A10 POOLED ESTIMATES OF GROUP MORBIDITY (Tot l illne s) $\bar{p}$ WITH ESTIMATED VARIANCES by ge gr up and numbe f home i its to 749 chil dren in the home-visit study

No of home-visits ( )	Age (months) 9–23 cv	p	p_k	10^5 (p_k)	24–59 cv	p	p_k	10^5 (p_k)	60–83 c	p	p_k	10^5 (p_k)
26	31	2581	2581	93 18	64	1538	1538	18 7	95	0538	0538	19 28
25	26	2231	2421	49 76	46	0583	1386	4 49	76	0353	0451	8 38
24	9	2824	.2476	43 15	38	1580	1348	1 77	38	058	0475	7 85
23	8	2228	.2449	38 01	11	1621	367	10 75	25	0426	0463	5 99
22	8	2443	2449	36 12	5	0909	333	10 46	2	36	0580	5 89
21	2	3333	.2478	35 01	8	1848	1334	9 86	6	03 7	0496	5 72
20	5	2900	2494	33 85	9	2167	377	9 48	9	0667	0502	5 53
19	2	3421	2514	35 37	2	3421	400	9 36	6	0077	0510	5 45
18	2	667	.2496	34 75	2	361	425	9 26	3	0370	0509	5 30
17	6	3 37	2535	33 34	6	.2157	425	9 00	9	0654	05 3	5 22
16	3	3958	2473	33 29	4	3544	494	8 82	8	0234	506	5 07
15	8	8	2473	33 29	4	.2333	5 2	8 66	1	0667	0506	5 05
14	4	5000	2565	34 37	5	5286	1647	8 48	2	07 4	0507	5 02
13	8	8	2565	34 37	8	0385	585	8 49	2	2308	0520	5 03
12	1	3333	2576	34 09	5	2000	645	8 37	4	250	0529	4 97
11	0	0	2576	34 09	2	2273	6	8 3		3636	0544	4 94
10	0	0	2576	34 09	0	0	6	8 3	0	0	0544	4 96
9	4	3054	2593	33 57	6		1557	8 32	7	0794	0545	4 91
8	1	7500	2637	33 39	6	0833	370	8 9	5	750	0565	4 85
7	3	429	2605	32 97	8	786	583	8 86	6	0338	0555	4 84
6	1	0	2583	32 83	6	389	570	7 98	4	0	0552	4 82
5	4	.2000	.2564	32 44	1	8 8	589	7 86	6	0375	0543	4 74
4	1	7500	2604	32 35	4	5000	1644	7 83	8	250	0560	47 2
3	2	0	2562	32 22	2		63	7 82	3	0	0533	4 7
2	4	2500	2560	32 07	2	0	6 8	7 8	3	667	0544	4 70
[illegible]	7	0571	2636	31 93	4	0	531	7 80	6	0	0533	4 70

TABLE A11. OBSERVED AND RECALLED NUMBER OF ILLNESS DAYS by day bef re ecall and by ecall period MSI(P_R P_O) mean squar inconsi t ncy measur s the degree f ov r- and und r-rec ll by ecall period (O bserved $\bar{O}$ = not bserved R ecalled $\bar{R}$ not ecalled)

Day before recall		2	3	4	5	6	7	8	9			2	3	4
r	192	92	92	92	93	92	192	88	88	88	88	88	88	88
OR	5	3	3		3		3	4	2	3	3	4	8	9
OR	5	7	5	6	9	7	6	7	20	3	22	25	26	22
OR	27	29	25	24		30	8	8	7	7	4	3		9
OR	135	33	39	4	40	43	45	35	39	35	39	134	11	30

Recall period		2	3	-4	-5	-6	7	-8	-9	0		2	3	
P_O	563	563	528	457	53	528	53	5 6	537	374	639	640	694	775
P_R	2 88	88	2 8	2044	979	1927	93	960	912	303	309	822	800	709
MSI(P_R, P_O)	2 80	2 35	883	836	685	571	496	385	300	276	1250	232	1 99	166
MS (%)	64	64	65	63	6	64	62	64	64	62	58	59	58	54
MSI (%)	36	36	35	37	39	36	38	36	36	38	42	4	42	46

Recall period	3	-4	3-5	4-6	5-7	8- 8	9-	8- 2	3 12	4
P_O	528	476	5	528	541	773	826	950	2092	2 99
P_R	2 8	1997	840	736	6 5	6 3	525	489	587	525
MSI(P_R, P_O)	2802	807	742	759	762	718	838	903	814	714
MS (%)	65	62	58	58	52	49	3	39	36	3
MSI (%)	33	38	42	42	48	5	57	6	64	69

TABLE A12 PERCENTAGE DISTRIBUTIONS BY VARIABLE SUB-CLASSES of the 411 households with 1020 children belonging to the BASE-LINE STUDY nd the 277 household with 749 children belonging to the MORBIDITY STUDY

COMPONENT	VARIABLE	CLASS	BASE-LINE STUDY 411 households	1020 children	MORBIDITY STUDY 277 households	749 children
HOUSEHOLD COMPOSITION	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
HOUSING	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

CULTURAL AND EDUCATIONAL CHARACTERISTICS	[illegible]	[illegible] [illegible] Other or no inform.	[illegible]
	[illegible]	[illegible] [illegible] [illegible] [illegible] Other or no inform.	[illegible]
	EDUCATION OF [illegible]	Illiterate Non formal education Formal education No inform. or "no answer"	[illegible]
	EDUCATION OF [illegible]	Illiterate Non formal education Formal education No inform. or "no answer"	[illegible]
HEALTH KNOWLEDGE AND ATTITUDES	[illegible]	[illegible] Knowledge about [illegible] [illegible] [illegible] [illegible] No inform.	[illegible]
	[illegible]	"Does not know" [illegible] [illegible] No inform.	[illegible]
	[illegible]	"Does not know" [illegible] [illegible] [illegible] No inform.	[illegible]
HEALTH PRACTICES AND USE OF HEALTH SERVICES	[illegible]	Performed Not performed No inform.	[illegible]
	[illegible]	Performed Not performed No inform.	[illegible]
	[illegible]	Performed Not performed No inform.	[illegible]
	[illegible]	Yes No "Does not know" or no inform.	[illegible]
	[illegible] CLINIC	Yes No Not known or not needed	[illegible]
	[illegible] CLINIC	Yes No Not known or not needed	[illegible]
PHYSICAL CHARACTERISTICS OF CHILDREN	SEX	Male Female	[illegible]
	AGE [illegible]	[illegible]	[illegible]
	[illegible]	[illegible] No inform.	[illegible]
	[illegible]	Yes No Not studied	[illegible]
	[illegible]	Yes No Not studied	[illegible]
	[illegible]	Yes No Not studied	[illegible]
	[illegible]	Yes No Not studied	[illegible]
	[illegible]	Yes No	[illegible]

TABLE A13 MEAN PEP CAPITA INCOME LEVEL in 256 households with different total income and six (Figures within brackets denote number of households)

HOUSEHOLD INCOME (Et $)	NUMBER OF HOUSEHOLD MEMBERS 2 3	4 5	6 7	8 9	10 14
50	15.06 (27)	9.00 (18)	6.15 (11)	4.72 (4)	4.80 (2)
50 100	25.00 (6)	16.94 (27)	11.83 (16)	8.85 (6)	7.25 (5)
100 300	66.67 (11)	46.06 (33)	31.17 (22)	23.29 (13)	19.02 (10)
300	211.11 (3)	121.67 (6)	75.52 (18)	56.37 (6)	56.69 (14)

TABLE A14 F equency distribution QUALITY OF HOUSING in 267 households acc rding t TYPE OF FLOOR CEILING WALLS and WINDOWS (267 of the 277 households included in the analysi of cute morbidity had complete information Cla s 1 lowe t quality For exact definitions of cl sses see Table A12)

VARIABLES AND CLASSES			WINDOWS Class 1 CEILING Class 1	WINDOWS Class 1 CEILING Class 2	WINDOWS Class 2 CEILING Class 1	WINDOWS Class 2 CEILING Class 2	WINDOWS Class 3 CEILING Class 1	WINDOWS Class 3 CEILING Class 2	Total	Grand total
FLOOR	Class 1	WALLS Class 1	16	0	64	5	0	1	86	89
		WALLS Class 2	0	0	3	0	0	0	3	
	Class 2	WALLS Class 1	1	6	21	62	3	63	156	178
		WALLS Class 2	5	0	1	0	0	16	22	
Total			22	6	89	67	3	80	267	
Grand total			28		156		83			267

TABLE A15 WATER CONSUMPTION in litres per ho sehold membe and d y BY SOURCE OF WATER P rc nt ge distri- buti of 234 household with omplet information i the mo bidity tudy

SOURCE OF WATER	WATER CONSUMPTION 5	5-10	10-20	20-	TOTAL %	Number of households
[illegible] tap	16.7	[illegible] 7	20.8	21.8	[illegible]	24
Shared tap	13.6	55.5	23.0	7.8	[illegible]	63
Bought from [illegible]	0	64.2	35.7	0	100.0	14
Common [illegible]	7.0	66.8	5	9	100.0	53

TABLE A16 AVERAGE MORBIDITY IN TOTAL ILLNESS ($\bar{p}_T$) GASTROENTERITIS ($\bar{p}_G$) AND RESPIRATORY ILLNESS ($\bar{p}_R$) IN SUB-CLASSES OF AID-PREDICTORS (Ag cl s ifications based on information from base-line survey in 1971 n_c = number of hildren $\hat{p}$ is weighted by the number f home visits)

COMPONENT	VARIABLE	CLASS	AGE GROUP IN MONTHS															
			[illegible]				[illegible]				[illegible]				[illegible]			
			n_c	$\hat{p}_T$	$\hat{p}_G$	$\hat{p}_R$	n_c	$\hat{p}_T$	$\hat{p}_G$	$\hat{p}_R$	n_c	$\hat{p}_T$	$\hat{p}_G$	$\hat{p}_R$	n_c	$\hat{p}_T$	$\hat{p}_G$	$\hat{p}_R$
HOUSEHOLD COMPOSITION	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
CULTURAL AND SOCIO-ECONOMIC CHARACTERISTICS	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
HEALTH PRACTICES	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
INDIVIDUAL CHARACTERISTICS	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

TABLE A17 SPLIT REDUCIBILITY (BSS/TSS IN %) IN THE AID ANALYSIS OF TOTAL ILLNESS by sub-gro p and predictor (= group is final only one sub-class Group numbers ref r to Fig re 40)

PREDICTOR	1	3	2	4	5	7	11*	8	6	13*	15*	12*	9*	14*	16*
NUMBER OF HOUSEHOLD MEMBERS	7 5	1 5	1.2	1 7	1	8	2	6	3	.0	.0	4	8	5	8
NUMBER OF CHILDREN UNDER 5	1 7	6	1	2	4	.8	3	5	8	0	8	1	.8	1	8
MARITAL STATUS OF PARENTS	8	6	6	4	8	1	0	0	4	8	8	8	8	-	8
AGE OF MOTHER I EARS	2 8	4	1 4	3	7	8	0	.8	0	0	0	4	0	1	8
HOUSEHOLD INCOME	1 1	1 2	9	9	5	1 9	5	8	1	-	8	1	1	2	8
NUMBER OF PERSONS/ROOM	2 0	1 3	2	1 2	5	6	5	6	1	.0	8	4	.2	6	8
LI ING AREA	3	6	1	7	4	1	3	9	8	.8	.8	8	8	1	8
TYPE OF FLOOR	2 5	1 4	7	6	6	8	3	5	3	.8	0	1	8	.6	.8
SOURCE OF WATER	1 8	2 2	8	1 3	8	3	5	6	1	8	8	1	2	4	8
WATER CONSUMPTION	1	1 6	1	3	1 4	3	1	3	1	8	.8	3	2	3	2
LATRINE STANDARD	2.8	1 4	3	1 1	4	8	1	8	3	.8	0	3	0	4	8
RELIGION	1 0	1 4	1	4	4	1	0	2	2	0	8	.8	0	1	8
ETHNIC GROUP	5	3	2	5	4	4	3	4	1	0	0	1	2	1	4
EDUCATION OF MOTHER	1	1	1	1	5	1	7	8	8	8	8	2	8	8	8
EDUCATION OF FATHE	1 8	1 1	4	5	8	4	6	9	.2	.8	8	1	1	0	8
UNULECTORY	2	3	1	2		2	.2	2	.8	.8	8	0	.8	1	.8
SEX	.8	.8	8	0	0	1	8	8	.8	.8	8	8	8	8	8
WEIGHT FOR AGE	20.5	1 4	1 9	1 1	6	4	7	6	-	0	0	2	3	2	8
AGE OF CHILD	20.6	3.6	2 1	2	0	3	8	.2	1	0	0	.2	0	1	8

TABLE A18 SPLIT REDUCIBILITY (BSS/TSS IN %) IN THE AID ANALYSIS OF GASTROENTERITIS by sub-group and pr dict r (group is final only one sub-class Gro p num- b r f to Figur 41)

PREDICTOR	1	3	2	5	4*	7	6*	8	11*	12*	9*	13*	10*
NUMBER OF HOUSEHOLD MEMBERS	5.0	3	1 2	4	3	8	3	3	3	.0	8	8	1
NUMBER OF CHILDREN UNDER 5	1 1	2	1	5	8	1	8	.0	0	.8	8	8	8
MARITAL STATUS OF PARENTS	1.0	8	1 2	0	8	8	6	.8	0	8	0	-	8
AGE OF MOTHER I EARS	2 9	8	5	1	.8	3	3	1	5	.8	8	8	8
HOUSEHOLD INCOME	1.0	1 6	4	5	.2	4	.2	1	.6	8	8	8	1
NUMBER OF PERSONS/ROOM	1 1	2	3	5	0	4	1	5	8	.8	8	8	.8
LI NG AREA	1	3	1	3	8	1	1	.8	3	8	8	8	8
PE OF FLOOR	1 3	8	3	1 8	1	4	1	8	1	8	-	8	2
SOURCE OF WATE	1 6	6	5	2	4	1 0	.8	0	-	8	8	8	1
WATE CONSUMPTION	8	1 1	1	6	2	8	1	5	1		0	8	8
L NE STANDARD	2 2	8	1 8	8	6	7	3	8	0	8	8	8	1
RELIGION	.8	8	2	8	8	1	1	8	8	.8	8	8	8
ETHNIC GROUP	5	8	2	5	5	1	3	3	3	.8	0	8	1
EDUCATION OF MO HE	1	5	8	3	8	.8	1	8	8	.8	8	8	8
EDUCA ION OF ATHER	8	5	9	1	6	5	3	1	1	0	8	8	8
ACCTURY	3	2	2	7	1	.0	1	1 0	1	8	8	-	8
SE	8	8	8	2	8	1	8		.8	8	.8	8	8
WEIGHT FOR AGE	16.0	2 2	2 8	8	1	3	2	3	2	.8	8	8	8
AGE OF CHILD	33.9	4	2 6	5	7	6	3	8	5	.8	.8	8	2

TABLE A19 SPLIT REDUCIBILITY (BSS/TSS IN %) IN THE AID ANALYSIS OF RESPIRATORY ILLNESS by sub-group and predictor (* = group is final ** = only one sub-class Group numbers ref. to Figure 42)

PREDICTOR	1	3	5	7	9	2*	4*	11	13*	8	10*	16*	6*	14*	12*
	GROUP NUMBER														
NUMBER OF HOUSEHOLD MEMBERS	1.2	1.1		.8	.6	.5	.5	.2	.2	.3	.1	[illegible]	.3	.8	.0
NUMBER OF CHILDREN UNDER 5	2.3	.3	[illegible]	.9	.1	.2	.2	.0	.0	**	[illegible]	**	.2	**	[illegible]
MARITAL STATUS OF PARENTS	.8	.8	.8	.0	.8	.0	.1	.8	**	.8	.8	[illegible]	[illegible]	**	[illegible]
AGE OF MOTHER IN YEARS	3.8	1.8	.3	.2	.6	.2	.1	.1	.4	.1	.4	[illegible]	[illegible]	[illegible]	[illegible]
HOUSEHOLD INCOME	.4	.5	.4	.4	1.4	.4	.3	.2	.4	.4	.2	.4	.1	.0	[illegible]
NUMBER OF PERSONS/ROOM	.4	1.8	.0	.2	.3	.8		.0	.2	.8	.8	[illegible]	.3	.8	[illegible]
LIVING AREA	.3	.6	[illegible]	.2	1.2	[illegible]	.7		.0	.2	.1	.8	.1	.8	[illegible]
TYPE OF FLOOR	.8	.2	.4	.6	.7	.4	.0	.0	.0	.3		.7	.8	[illegible]	[illegible]
SOURCE OF WATER	.7	1.5	1.2	.6	.9	.1	.5	.2	.8	.8	[illegible]	.5	.1	.8	.8
WATER CONSUMPTION	1.8	1.7	2.8		1.8	.3	.4	.3	[illegible]	1.3	.0	.8	.3	[illegible]	[illegible]
LATRINE STANDARD	.1		[illegible]	.3	[illegible]	.3		.8	.0	[illegible]	.8	.8	[illegible]	[illegible]	[illegible]
RELIGION	1.8	.7	1.2	[illegible]	[illegible]	.1	.1	.0	.0	.8	[illegible]	.0	.8	[illegible]	[illegible]
ETHNIC GROUP	.8	.7	.5	[illegible]	.6	.1	.7	1.3	[illegible]	.3	.2	[illegible]	.3	.8	
EDUCATION OF MOTHER	.6	.2	.0	[illegible]	.4	.8	.2	.0	.8	.8	.1		[illegible]	[illegible]	[illegible]
EDUCATION OF FATHER	.1	.1	.3	.4	.7	.1	.1	.0	.7	.8	[illegible]	[illegible]	.2	[illegible]	.8
VACCINATION	.3	.4	1.6	[illegible]	.6	[illegible]	.1	1.3	.8	[illegible]	.1		.3	[illegible]	[illegible]
SEX	.0	.1	[illegible]	.0	[illegible]	.8	.1	.3	[illegible]	[illegible]	.1	.2	.1	.0	[illegible]
WEIGHT FOR AGE	18.6	.6	.1	.1	.2	**	.3	.3	.1	.1	.4	[illegible]	.8	.8	.8
AGE OF CHILD	11.3	.4	.2	.1	.8	.4	.2	.2			.8	.3		.8	

TABLE A20 ESTIMATED LINEAR REGRESSION OF TOTAL ILLNESS AND GASTROENTERITIS ON AGE for sub-cl sses f AID-pr dictors for ll children and child en below 5 years p_T $\bar{p}_T$ $b_T(A\ \bar{A})$ and p_G $\bar{p}_G$ $b_G(A\ \bar{A})$ d ote the respective linear r gressions where $\bar{p}_T$ and $\bar{p}_G$ are mean Tot 1 and Gastroent ritis illness (in) b_T and b_G slopes of regressi n and $\bar{A}$ the averag age of childr n in ach b-class

[illegible]

TABLE A21 Characteristics of g oup split in AID-REGRESSION ANALYSIS OF MORBIDITY DUE TO GASTROENTERITIS (P_G cal l ted i %) ON AGE (A given in months) for 11 child en und r the g of 5 yea (TSS BSS RSS and BRSS v lue are multiplied by 10^{-4} Group numbe ref to Figu 53

Group characteristics		N	P_G = a + b(A–Ā)	TSS	RSS	RSS/TSS		BSS	BRSS		
( )–(2)–(3)	TOTAL SAMPLE	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]				
(2)–( )–( )	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]				
[illegible]								[illegible]	[illegible]	[illegible]	[illegible]
(3)–(4)–(5)	[illegible]	177	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]				
(5)–(6)–(7)	Shared tap, No before.	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]				
SOURCE OF WATER								[illegible]	[illegible]	[illegible]	[illegible]
( )–(12)–(13)	Private tap, Community tap	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]				
(6)–(10)–( )	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]				
[illegible]								[illegible]	1.80	[illegible]	[illegible]
(7)–(14)–(15)	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]				
(8)	Shared tap, Community tap	147	[illegible]	[illegible]		[illegible]	[illegible]				
SOURCE OF WATER								[illegible]	[illegible]	[illegible]	[illegible]
(9)	Private tap, [illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]				
(10)	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]				
INCOME								[illegible]	[illegible]	[illegible]	[illegible]
( )	[illegible]	[illegible]	[illegible]	[illegible]		[illegible]	[illegible]				
(12)	[illegible] 1/person	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]				
WATER CONSUMPTION								[illegible]	[illegible]	[illegible]	[illegible]
(13)	[illegible] 1/person	[illegible]	[illegible]		[illegible]	[illegible]	[illegible]				
(14)	Formal education [illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]				
EDUCATION OF [illegible]								[illegible]	[illegible]	[illegible]	[illegible]
( )	[illegible] formal education, No information	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]				
[illegible] reduction in variation [illegible]			[illegible]	[illegible]				[illegible]	[illegible]	[illegible]	[illegible]

TABLE A22 SPLIT REDUCIBILITY (BRSS/TSS IN %) in the AID-regressio analysis of Gastroenteritis on age by a b group and predictor in children aged und r 5 years (* group is final = only one a b-class)

PREDICTOR	GROUP NUMBER
[illegible]	[illegible]
[illegible]	[illegible]
[illegible]	[illegible]
[illegible]	[illegible]
[illegible]	[illegible]
[illegible]	[illegible]
[illegible]	[illegible]
[illegible]	[illegible]
[illegible]	[illegible]
[illegible]	[illegible]
[illegible]	[illegible]
[illegible]	[illegible]
[illegible]	[illegible]
[illegible]	[illegible]
[illegible]	[illegible]
[illegible]	[illegible]
[illegible]	[illegible]

TABLE A23 Per entag distribution of morbidity due t C troenteriti (p_G) in subcl se f THAID predictor (Age cl sifi ation based on inf rmation from ba eline survey in 1972) Roman fig r ref to mo bidity groups: I = 0-5 % II 5-10 % III = 10-20 % IV = 20- % The subcl sse of the predict r wer constructed using the d lta-crit ri n se p 108

VARIABLE	AGE 0-23 MONTHS: SUB-CLASS	n	I	II	III	IV	AGE 24-59 MONTHS: SUB-CLASS	n	I	II	III	IV
SEX	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
NUMBER OF CHILDREN UNDER 5 YEARS IN HOUSEHOLD	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
HOUSEHOLD INCOME PER ETB/MONTH	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
MARITAL STATUS OF PARENTS	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
AGE OF MOTHER YEARS	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
RELIGION OF HEAD OF HOUSEHOLD	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
ETHNIC GROUP OF MOTHER	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
LIVING AREA PER PERSON	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
LATRINE STANDARD	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
SOURCE OF WATER	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
WATER CONSUMPTION	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
ELECTRICITY	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
WEIGHT FOR AGE	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
EDUCATION OF MOTHER	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
EDUCATION OF FATHER	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
TYPE OF FLOOR	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
NUMBER OF PERSONS/ROOM	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
AGE OF CHILD	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
TOTAL	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

TABLE A24 Construction of the vari bl s used in the path analysis of morbidity due to Gastroenteritis

	[illegible]	[illegible]		[illegible]	[illegible]
	Mar[illegible] [illegible]	[illegible]ngle mothe[illegible] / Ma[illegible] f[illegible]		[illegible]	[illegible]
	[illegible]ucat[illegible]n of mother	Forma[illegible] education / [illegible] non-formal educat[illegible]on / [illegible]		[illegible]	[illegible]
[illegible]	Education of [illegible]	[illegible]rmal education / [illegible] non-forma[illegible] educat[illegible]on / [illegible]		[illegible]	[illegible]
	Household [illegible]	[illegible]ch individual [illegible] given the [illegible] / [illegible] values of [illegible] / ([illegible])		[illegible]	[illegible]
	[illegible]pe of floor	Bare ground / [illegible]	[illegible]	[illegible]	[illegible]
[illegible]	Source of water	[illegible]ivate [illegible] / [illegible]		[illegible]	[illegible]
[illegible]	Source of wate[illegible]	Commun[illegible] [illegible] / [illegible]	[illegible]	[illegible]	[illegible]
	Wate[illegible] [illegible]umption	[illegible] res or more/person/day / [illegible]/person/day [illegible]		[illegible]	[illegible]
	[illegible]	[illegible] / Other [illegible]		[illegible]	[illegible]
	Weight for age in % of Harvard [illegible]	[illegible]		[illegible]	[illegible]
	Age in months	[illegible]		[illegible]	[illegible]
	[illegible]	[illegible]		[illegible]	[illegible]
[illegible]	Source [illegible] weigh[illegible] for age	Shared [illegible] and [illegible] for age [illegible] / [illegible] / [illegible]		[illegible]	[illegible]
[illegible]	Source of [illegible]	[illegible] and water consump[illegible] / [illegible] or more/person/day / Other [illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible] and water consum[illegible] / [illegible] or more/person/day / Other [illegible]	[illegible]		[illegible]

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Body Composition, Cardiovascular and Renal Function in Adolescent Patients with Anorexia Nervosa

By LARS FOHLIN

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ACTA PÆDIATRICA SCANDINAVICA
SUPPLEMENT 268 1977

From the Department of Pediatrics Karolinska Institutet
St Göran's Children's Hospital, Stockholm, Sweden

BODY COMPOSITION CARDIOVASCULAR AND RENAL FUNCTION IN ADOLESCENT PATIENTS WITH ANOREXIA NERVOSA

by
Lars Fohlin

STOCKHOLM 1977

To fast – to study – and to see no woman
Flat treason gainst the kingly state of youth
Say can you fast? Your stomachs are too young
And abstinence engenders maladies

William Shakespeare
Love s Labour s Lost Act IV Scene III

CONTENTS

This survey is based on the following papers.

I Fohlin, L., Freyschuss, U., Bjarke, B., Davies, C.T.M. & Thorén, C.
Function and dimensions of the circulatory system in anorexia nervosa.
Acta Paediatr Scand, accepted for publication, 1977

II Davies, C.T.M., von Döbeln, W., Fohlin, L., Freyschuss, U. & Thorén, C.
Total body potassium, fat free weight and maximal aerobic power in children with anorexia nervosa.
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Thirty-one AN patients, 19 girls (mean age 14.9 yr) and 12 boys (mean age 14 7 yr) were studied at St. Goran s Children s Hospital, Stockholm, during 197 1977 All subjects were studied following informed consent by patients, control subjects and parents and after approval by the Ethical Committee of the Karolinska Institute All were under psychiatric treatment 29 of them having been at some time hospitalized at St. Goran s Children s Hospital. The criteria used for diagnosis were mainly based on those of Dally (13)

1 Age less than 25 years
2. Active refusal to eat, with accompanying pronounced weight loss
3 No evidence of schizophrenia severe depression or organic disease

It was not within the scope of this investigation *to distinguish between primary and atypical AN* as suggested by some authors (9 13) The selection of patients was influenced by several factors beyond the author s control, such as willingness to participate in the investigation and their physical and psychiatric condition The material may therefore not be representative of AN in the general population The higher proportion of boys (39%) in the present study [compared with a reported incidence of 5–10% (4 7 32)] may be a consequence of the selection procedure adopted

The patients were examined in collaboration with a senior psychiatrist The psychiatric and physical condition of the patients varied but non had a primary psychosis At the time of the study four of the patients were receiving medication (Thioridazin chloride Mallorol[R]) The patients physical characteristics are shown in Table 1

The patients lost weight by systematic refusal of food. The mean weight loss was .5% for boys and .6% for girls. Most of the patients had marked bradycardia and hypotension. Four of the girls developed symptoms before onset of menarche while the others had secondary amenorrhoea. Three of the boys showed no signs of puberty There was no anaemia, protein deficiency or clinical evidence of vitamin deficiency and all patients had plasma electrolyte values within the normal range (Table 2) The morning rectal temperature was low (Table 2) and only three of 23 patients had temperatures *over 36.5°C Weights prior to onset of AN were* obtained from school health records, the patients and their parents Only one patient had a history of overweight, i.e., weight-for-height of more than SD before developing symptoms of anorexia. Except for one boy and three girls the patients were at or below 2 SD on standard curves relating weight to height (6) (Fig. 1) One boy died of septichemia one year after the investigation

In study III, five and in study IV fourteen young healthy subjects were investigated as controls.

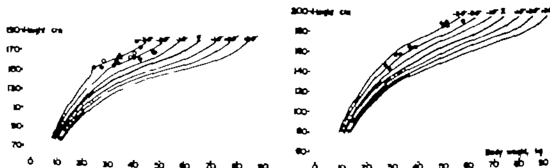


Fig 1 Relationship of weight to height in 31 AN patients. The standard height–weigh curves of normal healthy Swedish children are shown (6). Girls (o), boys (●).

Table 1 *Physical characteristics of the 31 anorexia nervosa patients*

Patients	Age (yr)	Weight (kg)	Height (cm)	Weight loss from premorbid weight (%)	Weight loss from predicted weight (%)	Duration (yr)	Study
Girls							
HH	12 1	30.0	153	15	33	0.5	I II III V
JJ	1 8	29.3	160	35	29	0 8	IV V
GZ	1_9	4.5	153	30	—	0.5	I II III
CW	13 1	39.0	163	35	29	0.5	I
BHj	13_	40.5	168	19	31	0 9	I
EA	13.3	33.5	157	14	30	0.5	I
ME	13.6	48.5	169	22	19	0.8	I III, IV
MSt	14.0	35 0	164	7	37	0 6	I II III V
CP	14_	34.5	157	15	_8	1.3	I, II III IV V
AS	14 8	4 9	173	25	31	1 0	I IV
YN	14 9	3_4	155	15	30	0.6	IV
GG	15 2	34 0	158	40	3	1.5	I, II III IV
AH	15.9	35 8	164	34	35	1 5	I II, III V
YS	16.6	48_	169	_6	19	_0	I II III
KA	16 7	38 0	173	3	39	0	I IV
PW	16 7	35.2	166	31	38	1 0	I II III IV
UN	16.9	41.8	180	_6	_0	1 0	I II III
LP	17 6	42.5	162	34	_2	0 6	I III
CA	17 7	40.5	163	33	6	3 0	I II, III
Mean	14 9	37 1	164	26	29	1 1	
SD	±1 8	±6 4	±7	±8	±6	±0 7	
Boys							
MM	11 3	28.6	14	38	16	0	I
JW	1 0	27.3	146	20	5	0 9	I II III
LK	12 5	31 0	156	1	29	1 0	I
PC	12.6	33 0	157	7	_5	1.0	IV
BG	13 7	50 6	188	_5	30	1 0	I
PW	14 0	38 5	164	_3	5	0 8	I II III
TG	15	36.6	164		_8	0.5	I
TL	15 9	36.3	164	30	39	1.0	I II, III
TT	16 0	56 7	187		20	0.8	I V
MS	17 1	51.0	184	—	27	1.0	I II IV V
UP	17.5	49.0	184	28	30	1 0	I IV
AN	18	48 7	186	—	31	1 0	I II III IV V
Mean	14 7	40 6	169	5	7	1 0	
SD	±_3	±10 1	±17	±5	±6	±0.3	

*From normal weight and height relation of Swedish children (6)

Table 2 *Clinical laboratory findings and morning rectal temperature. Mean (M) ± SD are given*

	Hemoglobin (g/l)	Protein (g/l)	Sodium (mmol/l)	Potassium (mmol/l)	Chloride (mmol/l)	Standard Bicarbonate (mmol/l)	Urea nitrogen (mmol/l)	Rectal temperature (°C)
M	138	73 0	140	4 1	104	_5.5	6.6	36.3
±	9	4.8	3	0 4	4	3	_0	0.5
n	31	7	29	29	_6	4	_6	_3

Detailed descriptions of the methods used are reported in the separate publications and are therefore only briefly summarized below

Circulatory dimensions and body compositions

Weight was measured with a clinical balance (Stathmos) accurate to ±100 g.

Height was measured with a stadiometer accurate to ±1 cm.

Heart volume (HV) was roentgenografically determined in the prone position (40) and *blood volume* (BV) was assessed with the ^{125}I-labelled albumin method (57)

1 -lead ECG was recorded with an Elema-Siemens recording apparatus.

Skinfold thickness was measured over the triceps and subscapular muscles with a Harpenden caliper (46 50)

Lean body mass (LBM) was calculated with the two skinfold methods of Parizková (46)

Whole body potassium (^{40}K) was determined in a whole body counter

Skeletal weight was estimated using the method of von Dobeln (19 20).

Fat free weight (FFW) was estimated from the determination of skeletal weight and whole body potassium (19 20) The percentage of body fat reported in the study was derived from measurements of skinfold thickness.

Exercise tests and aerobic performance

Exercise tests were performed in 28 patients sitting on an electrically-braked bicycle ergometer (Siemens-Elema) at a pedal rate of 60/min Usually two submaximal exercises were performed, with stepwise increases of the load before the maximal test The patients worked for 3-6 minutes t each load. The workloads were approximately 1 3 watts/kg body weight When possible a preliminary work-test was done in order to obtain information about their potential maximal wo king capacity Expired air was collected with Douglas bags and the volume was measured in a Tissot spirometer O_2 and CO_2 contents were analyzed by the micro-Scholander method for determination of *oxygen uptake* (VO_2) and respiratory quotient (RQ) During the exercise test heart rate was measured from ECG recordings *Lactate* (LA) was determined from blood obtained by finger prick and measured enzymatically (11) It was not possible to apply the accepted criterion for maximal VO_2 i e reaching a plateau of VO_2 w th increasing work-loads Instead, secondary riteria based on LA> 9 mmol/l and RQ ex eding 1 0 were used (3) The patients were enc u aged t cont nue the exercise to exhaustion Seven of 28 patients failed to perform maximal work.

Six of the patients repeated exercise tests and *cardiac output* and *stroke volume* were determined using the dye dilution technique with indocyanine green (Cardiogreen®) as the indicator substance and with a Beckman densitometer as the recording unit. The dye was injected into a cubital vein. Arterial blood was taken from a cannula inserted into the brachial artery Dye dilution curves were calculated by the method of Kinsman et al (39).

Renal function

The glomerular filtration rate (GFR) and *the renal plasma flow* (C_{PAH}) were determined by the clearance of inulin and PAH respectively using continuous infusion of inulin and PAH Urine was sampled by spontaneous voiding, and to ensure a constant urine flow the patients were allowed to drink water in an amount of 0.25% of body weight every half hour In general clearance periods were 1 hour Blood and urine samples were analyzed for inulin, PAH urea, sodium and osmolality Inulin was determined by the Anthron method (33) PAH was determined by the method of Smith et al (49). Urea nitrogen serum and urine were determined by analyzing ammonia calorimetrically before and after the action of urease (?6) The GFR was expressed in terms of body surface area on both the patients and the control children, both groups were of similar age and height.

Maximal urine osmolality was determined in a Knauer osmometer after 17 hours of fluid and food deprivation with and without exogenous pitressin in a dose of 0.5 pressor units/6 kg of body weight.

Peripheral circulation

Lower limb circulation and the effects of localized radiant heat on calf blood flow were measured by venous occlusion plethysmography (16 31).

Digital pulse plethysmography was recorded from the first toe Skin temperature was measured at 5-6 levels on the lower limb and was recorded before and after indirect heating The control group consisted of 14 healthy school children matched by age and height with the anorexic patients.

Body composition (II)

Average percent weight loss calculated from premorbid weights was 26% for the girls and 25% for the boys (Table 1). Corresponding figures obtained from the patients' predicted normal weight were 29% and 27% for the girls and boys, respectively. The majority of the patients were SD (according to Swedish growth curves) below normal values relating weight to height (6).

Fifteen of the anorexic patients (five boys and ten girls) were studied with calculations of FFW derived from total body potassium and lean body mass estimated from skinfold thickness (Table 3). Mean values for triceps and subscapular skinfolds were 5.4 and 4.6 mm in the girls and 3.4 and 4.0 mm in the boys. These values are outside the lower normal range (50). Estimates of percentage fat tissue of body weight averaged 6.4% in the boys and 8.5% in the girls.

Total body potassium correlated well with body weight in both groups of patients. In absolute figures ^{40}K was low but the mean values of 2.12 and 2.10 g per kg body weight in boys and girls, respectively are within normal limits (10 21). There was no evidence of a reduction in skeletal mass, since the percentage skeletal weight of body weight was higher than expected compared to the normal adult relationship (18). FFW (calculated from ^{40}K and skeletal weight) showed a significant correlation to LBM (calculated from skinfold thickness) ($r = 0.97$, $p < 0.001$).

Physical and circulatory characteristics at rest (I)

Four patients had inconstant inversion of T waves over the left precordium. Only four patients had heart rates faster than 60 beats/min. The mean heart rate was 53 beats/min (37 75) (Table 4). The recordings of heart rate cannot be considered as basal as they were obtained just prior to the exercise test. Shortly before the investigations four patients had bradycardia of about 30 beats/min. The lowest heart rate recorded was 28 beats/min. Sinus rhythm dominated, but periods of arrhythmias, such as sinus arrests and ectopic atrial rhythm were recorded. Blood pressure at rest was low with a mean of 96/67 mm Hg.

Heart volume was significantly correlated to blood volume ($p < 0.001$). Both of these parameters were low as compared with healthy children of similar age (37 53). The decrease in blood volume however was proportional to the weight loss, with a mean value of 74 and 81 ml per kg body weight for the girls and boys, respectively. Similar findings were noted when heart volume was related to body weight. The majority of the observed values were within the normal range (53).

Circulatory adaptation to exercise and maximal aerobic power (I, II)

During exercise heart rate increased linearly with increasing work load, but heart rate was lowered for given relative VO_2. The maximal heart rate was low and averaged 175 beats/min (Table 5). Blood lactate increased during work to level normal for healthy children of similar age (53). Since the VO_2 was low for a given work load and reduced to the same extent as the oxygen consumption at rest, there was no evidence of increased mechanical efficiency.

In six patients cardiac output was measured during submaximal exercise. In absolute terms the cardiac output was decreased at rest. The cardiac output, however was normally related to oxygen uptake (25) indicating a normokinetic circulation. The calculated stroke volume was normally related to the patients' blood volume (compared to adult values) (34) and well maintained during work.

Maximal oxygen uptake (VO_2 max) averaged 1.38 l/min in the boys and 1.21 l/min in the girls (Table 5). In terms of body weight, this represented a VO_2 max of 35 ml/kg per minute and 32 ml/kg per minute. These values are well below the normal range for healthy children (52). When VO_2 max was related to heart volume it was found to be lower than normal (53). VO_2 max was also low (46) when expressed in terms of per kg LBM and averaged 38 ml/kg (LBM) per minute in the girls and the boys. Thus the decrease in maximal aerobic power was greater than expected even with due consideration paid to body weight, lean body mass and circulatory dimensions (heart and blood volume).

Table 3 *Skinfold thicknesses, percent body fat and total body potassium (^{40}K). Mean (M) ± SD are given*

	Triceps (mm)	Subscapular (mm)	Fat (%)	^{40}K (g)	^{40}K (g/kg)
Girls					
M	5.4	4.6	8.5	75.7	2.10
± SD	1.5	0.9	3.5	11.4	0.24
10					
Boys					
M	3.4	4.0	6.4	81.5	2.12
± SD	0.6	0.8	2.3	11.8	0.22
5					

Table 4 *Circulatory data obtained at rest. Mean (M) ± SD are given*

	Heart rate (beats/min)	Blood pressure Systolic (mm Hg)	Diastolic	Heart volume (ml)	Blood volume (l)	(ml/kg)
Girls						
M	54	96	65	428	..76	75
±SD	10	9	5	76	0 47	13
n	19	19		19	16	16
Boys						
M	51	96	67	547	3.27	81
±SD	11	9	6	136	0 79	14
n	12	12		9	12	12

Table 5 *Data obtained at maximal work load. Mean (M) ± SD are given.*

	Heart rate (beats/min)	Oxygen uptake (l/min)	(ml/kg×min.)	Blood lactate (mmol/l)	Respiratory quotient
Girls					
M	174	1.21	3	11.8	1 14
±SD	8	0 18	5	2 1	0.07
n	13	13	13	13	13
Boys					
M	175	1.38	35	12.6	1 18
±SD	6	0.33	3	2 1	0.07
n	8	8	8	8	8

Table 6 *Renal hemodynamics and urinary concentrating capacity*

	GFR (l/hr)	(l/hr/1 73m²)	C_{PAH} (l/hr)	(l/hr/1 7
Patients				
M	3 54	4 37	23..8	28.69
±SD	0 71	0 74	5.66	5 71
n	12	12	1	1
Controls				
M	5 77	6 [illegible]0	..6.36	29.26
±	0 89	0 56	1 45	2 13
n	5	5	5	5
P	<0 001	<0 001	NS	NS

NS not signif ant

Peripheral circulation (III)

In 16 of the patients blood flow skin temperature and blood pressure in the lower limbs as well as the effect of radiant heat on calf blood flow and leg skin temperature were determined. The results were compared with healthy controls matched for age and height. In the anorexic group the calf blood flow was significantly reduced compared with controls. Blood flow in the lower limbs increased significantly after exposure to indirect radiant heat in both the anorexic and the control subjects, but the increase was less marked in the patients. Blood pressure and the skin temperature over the knees and toes were lower in the anorexic children The digital pulse plethysmogram, however was similar in both groups. The low limb flow and the impaired circulatory response to heat exposure in the anorexic patients indicate increased peripheral vascular tone

Renal function (IV)

Renal function was determined in twelve of the patients, eight girls and four boys. The results were compared with those from five healthy control subjects of similar age The serum protein concentration was normal in AN but slightly lower than in the controls. GFR was significantly reduced in the anorexic group and averaged 3.54 l/hour (range 2.30 4.63) and 4.37 l/hour/1 73 m^2 body surface (range 3.56 5 72) (Table 6). Mean C_{PAH} was slightly but not significantly lower in AN patients. The filtration fraction (FF), the quotient between GFR and C_{PAH} was, however significantly reduced in AN The individual variation of C_{PAH} was great, but there was significant correlation between GFR and C_{PAH} The good correlation between GFR and C_{PAH} indicates that reduced renal plasma flow must be one of the factors contributing to the decline in GFR However the decrease in GFR was out of proportion to the decline in renal plasma flow as indicated by the low FF The mean blood pressure in the anorexic patients was significantly reduced but there was no correlation between FF and blood pressure The decrease in GFR must therefore be ascribed to other factors The depression of the FF was well related (0 75 $p < 0 01$) t the severity of the disease (expressed as per cent weight loss)

Maximal urinary osmolality (Table 6) following 17 hours fluid deprivation was moderately depressed The administration of exogenous ADH did not significantly increase or normalize the maximal urinary osmolality Fractional N and urea clearance did not differ from that found in the controls

Effect of rehabilitation on body composition and circulation in AN (V)

The circulatory system and body composition were studied in eight patients following weight gain resulting in a normalization of weight. The average duration of the rehabilitation period was 1.5 years. The height of the patients remained unchanged during this period of observation. Heart and blood volume increased significantly in proportion to body weight in all patients after normalization of weight LBM was significantly higher at the second examination indicating that the reduction in weight results not only from the loss of adipose tissue but also from a decrease in fatfree tissue After normalization f weight, the heart rate at rest returned to normal in all patients with an average value of 79 beats/min.

The heart rate increased from the AN value f 177 beats/min to 195 beats/min at maximal exercise Similarly the oxygen uptake increased in all patients from a mean of 36 ml/kg to 46 ml/kg. There was no difference in the maximal blood lactate values before and after rehabilitation. The VO_2 max which was out of proportion to body composition and circulatory dimensions (heart and blood volumes), returned to normal values after rehabilitation.

The effect of semi-starvation on adult male subjects has been thoroughly discussed by Keys et al in their monograph The Biology of Human Starvation (38) and it is reported that caloric restriction has a considerable effect on body-structure and function The effect of AN on body composition is striking. It is obvious from the present results that reduction in adipose tissue is only partly responsible for the weight loss indicated by the reduced LBM The formula used to estimate LBM (46) can be criticized since it was based on findings in healthy children aged 8–13 years old However when this method was compared to the ten skinfold method of Parizková (46) based on findings in children up to 16 years old, similar results were obtained. The estimate of LBM from skinfold thickness was in good agreement with FFW calculated from total body potassium (^{40}K) and skeletal weight The reference material estimating FFW from ^{40}K and skeletal weight was based on healthy subjects (19 20) who were older than the AN patients in this study

The decrease in body fat with subsequent loss of thermal insulation in AN results in the need to minimize heat losses from the body In the AN patient this need is reflected in active peripheral vasoconstriction This study and data on thermoregulation during prolonged exercise using the same patient material (15) suggest that altered thermoregulation is a result of loss of insulation and do not indicate any primary hypothalamic dysfunction f the thermoregulatory system in AN as suggested by others (44 55)

This study provides evidence f a reduced GFR and slightly reduced C_{PAH} As the reduction of GFR was out of proportion to the reduction of C_{PAH} the filtration fraction (FF) was markedly reduced It is therefore ob ious that reduced plasma flow is not solely responsible f the reduced GFR and that some the factor must be m h d The ultra filtration pressure is deter n d by the diffe nce between hydrostatic and oncotic pressure in the glomerular capillaries and therefore depends mainly on arterial blood pressure and serum protein content Although the arterial blood pressure was reduced in the AN patients there was no correlation whatever betwee arterial blood pressure and FF As the serum protein content was found to be normal it is obvious that some other factor must contribut t the educed GFR A reduction in the size of the glomerular capillary bed is unlikely and t is therefore suggested that in AN an unknow mechanism causes an alteration e decrease in the w ter permeability of the capillary wall It is possible that the catabolic state in AN where protein depriv tion is not predominant, alters the molecular composition of the capillary wall so that its water permeability decreases. The good correlation between the severity of the disease (expressed as % weight loss) and FF provides indirect evidence for this hypothesis. If generalized, a decreased water permeability of the capillary wall has some bearing on the edema not infrequently seen in AN Hence the edema might be explained by a reduced ability to reabsorb fluid from the interstitium to the venous side of the capillaries. Edema is thus likely to occur whenever endogenous water production increases. In addition, the reduced GFR contributes to fluid retention.

Although no pronounced reduction in concentration capacity could be demonstrated in any of the AN patients studied, the maximal urine osmolality was, in general somewhat lower than in the controls. Similar abnormalities have previously been reported in both experimental starvation (38) and in AN (44) As the AN patients in this study did not normalize their concentrating capacity following the administration of vasopressin, it is suggested that the concentrating defect is of renal rather than central origin. The exact nature of the renal concentrating defect is not known. However a defect in two of the three factors that are generally assumed to determine renal concentrating capacity can be ruled out namely

1 a defect in sodium reabsorption from the loop of Henle as evidence by a normal fractional Na clearance and
 a defect in the recycling of urea from the collecting duct to the medullary interstitium and loop of Henle as evidenced by a normal fractional urea clearance and normal to slightly increased serum urea levels. A defect of the third factor osmotic diffusion f water from the collecting duct to the renal interstitium and the asa recta is more likely to be implied, and reduced water permeability of the collecting duct and/or the asa recta may contribute to the reduced concentrating capacity

Studies in progress provide evidence that the renal abnormalities demonstrated i this study are reversible and therefore suggest an adaptive mechanism Complet normalization of renal function was demonstrated after reh bilitation of some of the patie ts The advantage of such an adaptation, invol ing decrease of GFR and renal plasma flow would be t reduce the renal work load and minimize energy consumption

Whatever the nature of the renal abnormality in AN t is f r clinical reasons important to be aware of the altered enal homeostasis particularly in situations where losses of fluid and electrolytes are extreme and where there is need for intravenous fl id and electrolyte therapy

The normal adaptation of heart and blood volume to body weight before and after weight gain found in this study partly conflicts with the results of the Minnesota experiment (38) where blood volume hardly declined after 24 weeks of semi-starvation. For obvious reasons many factors could be expected to influence this adaptation: age of the subjects, degree of physical activity and duration of the disease. The latter factor is most likely responsible for the discrepancy in results mentioned above. It should be noted that the mean duration of weight loss in the AN patients was 1.1 years.

The ECG abnormalities, such as lower voltage, bradycardia and T wave inversion recorded at rest in this study have previously been reported in experimental starvation (38) and in AN (54). The pathogenesis of the T wave inversions remains unknown. There was no derangement of the serum electrolytes that could explain the ECG findings, although intracellular changes could not be excluded. ECG abnormalities of similar type are described in hypothyroidism.

In six patients, T wave inversion was recorded during exercise. In one patient similar changes during an orthostatic test were eliminated by the administration of β-receptor blocking agent. This indicates a functional rather than an organic origin.

The responses to exercise showed that the max. heart rate and VO_2 max was low. The decrease in VO_2 max was greater than expected, with regard to weight loss, lean body mass and circulatory dimensions (heart and blood volume). The reduction in VO_2 max in the present study is in good agreement with the results of the Minnesota experiment (38) where VO_2 max per kg body weight declined 26% in nine adult men following a 24% weight reduction. It cannot be determined whether the decreased VO_2 max is a consequence of a lowered resting metabolic rate or/and an effect of reduced muscle mass. From the respiratory quotient and blood lactate values, it may be assumed that the AN patients in reality performed maximal aerobic work, and that would exclude that the low VO_2 max was due to suboptimal maximal work because of poor motivation for the test.

The low maximal heart rate of the AN patients is hard to explain. The reduction of muscle mass found in AN, which contribute to loss of strength, undoubtedly affects the ability to perform maximal aerobic work and may result in a low maximal heart rate. A further possibility would be that the habitual low body temperature contributes to the low maximal heart rate, as is the case in maximal exercise during experimental hypothermia (14). The low maximal heart rate may also be a reflection of the bradycardia seen at rest.

The effect of caloric restriction on body structure and function found in the present investigation is in good agreement with previous investigations of experimental semi-starvation. The bradycardia, hypotension and hypothermia found in AN patients are also reported to occur during long-standing caloric restriction (38). The reduction in maximal physical performance is of similar magnitude to that found in the Minnesota experiment (38). Heart and blood volume in the AN patients showed a more marked adaptation to body weight than results obtained from the Minnesota study (38). Regarding body composition following weight loss, there was a decrease in LBM in the AN patients. Similar findings have been reported from dietary treatment of obese subjects (41) and in the Minnesota experiment (38).

A reduction in GFR such as found in AN patients is also reported in malnourished children (1), protein deficiency (4) and dietary weight reduction of obese patients (43).

All these results would suggest that the pathophysiological findings in the AN patients in this study may reflect the reduced energy supply per se. A comparison with other forms of undernutrition is for many reasons hard to make since there are few detailed studies of the pathophysiology of other types of starvation. The investigations referred to were also entirely based on results from subjects of different age than the AN patients studied. However, the pathophysiological findings in the AN patients appear to indicate a functional adaptation to a decreased caloric supply. The parameters studied were totally normalized following rehabilitation with weight gain to normal and premorbid levels. This shows a great capacity for adaptation in the adolescent AN patient. None of the findings in the present investigation supports the hypothesis of a primary hypothalamic dysfunction in AN (44, 55). It is possible that the borderline between primary AN and "simple weight loss" in the adolescent period is vague with a gradual development of the pathophysiology into the classic form of AN.

Attempts were made to evaluate the degree of severity of AN. Although a good correlation was found between FF and percentage weight loss, no correlation was found, for example, between heart rate, body temperature, peripheral blood flow, GFR and the degree of emaciation, estimated as per cent weight loss or per cent adipose tissue. It is suggested that many factors are involved in the adaptation to decreased energy supply and that the adaptation is not a rectilinear function of weight loss.

From this study it is concluded that the self-induced caloric restriction seen in anorexia nervosa results in considerable changes in body composition and circulatory and renal functions. From the clinical point of view it is important to be aware of the adaptations that follow weight loss in these patients. The loss of weight was not due solely to a loss of body fat, but could also be ascribed to a decrease in soft fat-free tissue. The reductions in heart volume, blood volume and total body potassium were found to be proportional to the weight loss.

The findings of low body temperature and loss of body fat suggest a potential risk of hypothermia. This is of particular importance when the patients are exposed to a cold environment.

It should be emphasized that these patients have a very low aerobic capacity, despite their often marked hyperactive behavior. This implies that the AN patients during daily life, when activities often require an oxygen uptake of around 1 l/min, work close to their maximal capacity.

The renal dysfunction found in this study is probably of minor importance in daily life. However, during abnormal situations such as gastroenteritis or intravenous treatment, it is necessary to consider the altered renal homeostasis and the adapted circulatory dimensions. The edema sometimes found in anorexia nervosa is consistent with the presence of a reduced GFR and a possibly generalized decrease in membrane permeability. When water production is increased, these factors contribute to fluid retention.

The somewhat broad criteria for AN in this study may be open to criticism. Nevertheless, an early recognition of the syndrome is important for the prognosis (29). This may justify a broad definition of the disease.

GENERAL SUMMARY

The main results of this investigation are as follows

1. Thirty-one patients, 19 girls (mean age 14.9 yr) and 12 boys (mean age 14 7 yr) with anorexia nervosa were studied The average weight loss from the premorbid state was 26% in the girls and 25% in the boys.
2. There were no signs of anaemia or protein and vitamin deficiency
3. All except four patients had bradycardia below 60 beats/min. The majority also had low blood pressure and low body temperature
4. Heart and blood volumes were below the expected range for children of similar age These parameters were however normally related to body weight.
5. Cardiac output was related to oxygen uptake in a manner indicating normal kinetic circulation. Stroke volume was normal and well maintained during exercise
6. Total body potassium in absolute terms was low but within the normal range when related t body weight
7. Triceps and subscapular skinfolds were below and well outside the range described for healthy children. LBM calculated from skinfold thickness, and FFW determined from ^{40}K and skeletal weight, were similar and significantly correlated Thus the former could be used as reliable indication of LBM in clinical conditions
8. Maximal oxygen uptake was decreased more than could be expected from the loss of body weight, or the changes in circulatory dimensions (heart and blood volume) and lean body mass. The decreased VO_2 max was associated with low mean maximal heart rate
9. Peripheral blood flow and skin temperature were lower than normal but increased, although less than in the control subjects, after indirect heating. There was evidence of increased peripheral vasoconstrictor tone in the lower extremities. It was suggested that these alterations might be a physiological adaptation due to loss of thermal insulation.
10. Glomerular filtration rate and filtration fraction were both reduced in relation to control values. Maximal urinary concentrating capacity was subnormal and there was no significant increase following the administration of exogenous ADH. The reduction in GFR could not be explained only in terms of a decreased renal blood flow and it was suggested that renal dysfunction was due in part to a reduced membrane permeability
11. Eight of the patients were studied again after therapy which resulted in a regain of their normal weight Maximal oxygen uptake and heart rate were increased to within the normal range Heart and blood volumes increased proportionally to the gain in weight. LBM calculated from skinfold measurements increased significantly during recovery Thus all studied parameters were found to be normalized following restitution of the normal body weight

From this study it is concluded that the self-induced caloric restriction seen in anorexia nervosa results in considerable changes in body composition and circulatory and renal functions. From the clinical point of view it is important to be aware of the adaptations that follow weight loss in these patients. The loss of weight was not due solely to a loss of body fat, but could also be ascribed to a decrease in soft fat-free tissue. The reductions in heart volume, blood volume and total body potassium were found to be proportional to the weight loss.

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ACTA PÆDIATRIC SCANDINAVIC

SUPPLEMENT 259

Cystic Fibrosis – A Psychological [illegible] of 52 Children and their Families

By CECILIA FALKMAN

ALMQVIST & WIKSELL [illegible]

ACTA PÆDIATRICA SCANDINAVICA, SUPPLEMENT 269

Cystic Fibrosis — A Psychological Study of 52 Children and their Families

By Cecilia Falkman

Medical advisor: Hans Kollberg

UPPSALA 1977

LiberTryck Stockholm 1977

TO HENRIC

While CF is a disease
not easy for parents to
live with, how much more
difficult it must be for
the child

LiberTryck Stockholm 1977

CONTENTS

As the mother of a child with Cystic Fibrosis I have myself experienced many of the problems discussed in this investigation. With the awareness of the vast difficulties that the raising of a child with a chronic disease constitutes, and with the very strong desire to give my own son the best possible care, both medically and psychologically and to develop in him a healthy personality the study of different aspects of Cystic Fibrosis has been important to me. Later this gave me the initiative to the present investigation, which, I sincerely hope, might help improve the total management of the chronically ill child.

The fact that I am the mother of a CF child has been both an advantage and a disadvantage in pursuing this study The unique rapport with the mothers which was made possible has by far out weighed the disadvantage, this being the risk of interviewer bias. I have, however been very well aware of the risk and have done my utmost to guard myself against it (50).

I. INTRODUCTION

Cystic Fibrosis

"Wehe dem Kind,
dass beim Kuss auf die Stirn
salzig schmekt,
es ist 'verhext'
und muss bald sterben."
(From midieval Swiss and German folklore)

Definition

Cystic Fibrosis (CF) is a hereditary disorder in which there is a widespread dysfunction of the exocrine glands. Classically chronic pulmonary disease, pancreatic enzyme deficiency and abnormally high sweat electrolytes are present. The disorder is characterized by different degrees of involvement of affected organs and glandular systems which results in a great variation in the clinical expression of the disease.

Incidence

CF is one of the more common of the serious chronic diseases of childhood and adolescence and is the most frequent lethal genetic disease among white children. It is a disorder primarily of the Caucasian race. Numerous cases have, however been found in black Americans and well documented cases have also been reported among other races (120). The incidence of the disease among Caucasians has, in numerous studies, been estimated to 1:1000–1:4000 live births (120), and in Sweden to 1:3000 (63). The carrier incidence has been estimated to lie between 3 to 6 % of the population. There is no apparent sex difference in the incidence.

Genetics

The basic defect of CF is still unknown. It is, however known that the disease is genetically transmitted as an autosomal recessive trait (Mendelian recessive trait). The risk of the disease occurring in subsequent children to parents who have earlier born a CF child is thus one in four each conception having the same 25 % chance of producing an affected child, regardless of the outcome of previous pregnancies. The pattern of transmission is shown in fig. 1

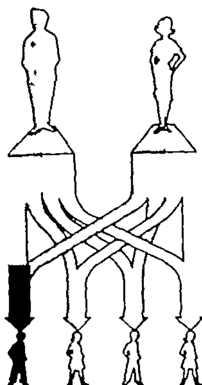
The homozygotes show the clinical picture of CF while the heterozygotes have no known clinical manifestations. So far there has not been any generally reproducible laboratory tests to identify the heterozygotes. The studies by Höll and Kollberg of a leakage of lysosomal enzymes may however give a heterozygote test within short (Kollberg, H., personal communication).

Symptoms

The dominating problem for the CF patient is a viscous bronchial secretion which is very difficult to remove from the lower airways. The respiratory system is susceptible to many serious complications, such as bronchial obstruction, atelectasis, bronchiectasis, recurrent respiratory infections and eventually fibrosis of the lung. The earliest symptoms referrable to the bronchial system is increased respiratory rate and [illegible] a dry and non-productive cough. At [illegible] no more than a frequent clearing of [illegible]

HEREDITARY FACTORS

When both parents carry the CF gene

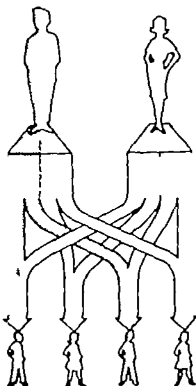


1 Child in 4 will have CF

2 Children in 4 will carry the CF gene

1 Child in 4 will not carry the CF gene

When one parent carries the CF gene and one parent is normal



2 Children in 4 will carry the CF gene

2 Children in 4 will not carry the CF gene



Fig. 1 The pattern of gene transmission.

may be spasmodic in nature and may be associated with vomiting. Following an acute respiratory infection, signs of bronchial obstruction and secondary bacterial infection frequently occur. Many patients have a continuous, productive cough with discoloured and viscous sputum. It may sound like whooping cough. There are nearly always potential pathogenic bacteria in the CF patients airways (47 72). As a rule Staphylococcus aureus first appear followed by Pseudomonas aeruginosa. Klebsiella pneumoniae, Hemophilus influenzae and Proteus species are

also found but less frequently. Infections are continuously recurrent and very difficult to combat. *They give rise to increased secretion which is even* more viscous and difficult to remove. Chronic *sinusitis and nasal polyps which tend to recur after* surgical removal are other common symptoms *from the respiratory tract of the CF patient.*

The earliest complication, occurring in 7–8 % of newborns with CF is *meconium ileus*. A viscous meconium obstructs the intestinal canal. Surgery is very often required.

Most CF patients have a pancreatic enzyme deficiency already at birth resulting in a *failure to* increase in weight and a failure to thrive. After a few years the enzymes are completely or partly absent in 90 % of the patients (103). The patients suffer from malabsorbation with frequent, bulky voluminous and fatty stools. Rectal prolapses occur in approximatly 25 % of all cases, usually prior to the diagnosis. Many patients suffer from recurrent abdominal pains. Signs of secondary vitamin deficiency especially of the fat-soluble vitamins A, D E and K may occur.

In all patients with very few exceptions the concentration of chloride and sodium in body sweat is increased from 2 to 5 times the normal level (105). The bile has an increased viscosity which may give rise to clinical symptoms such as prolonged jaundice in the newborn and biliary cirrhosis of the liver in elder patients.

Diabetes mellitus is being seen with increasing frequency among CF patients. The mounting incidence is associated with the greater longlevity of the patients and is noted mainly in adolescents and young adults (46).

Puberty is often delayed in both CF boys and CF girls. Most CF men are sterile, but a few fathers have been reported (28, 109). CF women *are fertile, even if their fertility probably is* somewhat decreased due to viscous cervical secretion (92).

Diagnosis

The diagnosis of CF is generally established by a positive sweat test, confirmed by a second test, in combination with objective evidence of the typical pancreatic involvement *or* objective evidence of the typical pulmonary involvement *or* a family history of CF confirmed by sweat test (105).

Treatment

As the basic defect of CF is still unknown, treatment must be aimed at reducing the symptoms and at trying to avoid complications. As the clinical picture is very varied both inter- and intra-individually an individual treatment program must be established. The treatment is extensive and very time consuming. Treatment of the airways include mucus liquifying by expectorants, nightly mist tents and/or inhalations of mucolytic aerosols. The mucus liquifying treatment must always be combined with mucus removing treatment–postural drainage, chest physical therapy with ventilation of the lungs, breathing exercises and physical activity of different kinds. The aim is to try to inhibit damage to the lungs. The treatment usually takes 30 minutes to 1 hour to perform and must very often be repeated several times a day. In order to try to control pulmonary infections, proper antibiotics, chosen preferrably after culture and sensitivity tests, are given at high dosage levels and for adequate periods of time for every active infection. Vaccinations against respiratory diseases such as influenza, morbilli and whopping cough are always recommended.

The treatment of the nutritional symptoms include substitution of pancreatic enzymes, a diet high in proteins and calories but low in fat, and supplementary vitamins, especially the fat solulable vitamins A, D E and K.

Prognosis

As CF exhibits considerable variation in severity of clinical manifestations, so must individual prognosis vary. In general, the outlook depends almost entirely on the course of the pulmonary lesion (105). This in large measure is determined by the degree of damage at the time of diagnosis and initiation of proper therapy (105). The importance of early diagnosis is crucial in prognosis and can not be overemphasized.

Research into CF is carried out in many parts of the world. This has resulted in a good current

understanding of the pathogenesis of the disease which in turn has led to more effective methods of treatment. The outlook for patients with CF has improved considerably during the past two decades and the life expectancy is increasing for every year at the passes.

General considerations

Many of the psychologic consequences that are found in a child with CF or in its family are not unique for the disease. The problems of anxiety the phenomenon of defense mechanisms and the process of coping behaviour in both child and parents are common reactions to chronic illness, and the characteristics shown in one illness can often be generalized to others. The total sum of characteristics is, however always unique.

The CF child is often small, and may have little physical strength and may tire easily in comparison to healthy peers. These symptoms are shared with children with other disabilities. The small body size, the late somatic development and late onset of puberty of the CF child may lead a negative body image, as found e.g. in children with cardiac diseases (39), transplanted kidneys (51) and diabetes (31).

The CF child coughs, sometimes more or less continuously and the cough may often keep it awake at night. Asthmatic children may have the same symptoms. The sputum the CF child must cough up is often a source of embarrassment. Because of the sputum and because of fear of contagiosity the cough may isolate the CF child already when he is very young.

Another source of embarrassment, unique for the CF child, is its foulsmelling stools which often makes it reluctant to go to the toilet away from home. Clubbed fingers, also found among e.g. cardiac children, is also often a source of embarrassment.

The CF patient needs a considerable amount of therapy and physical assistance which involves being dependent upon others. In this respect the CF patient may be compared to children with cerebral palsy and to children with auditory or with visual impairment.

The CF child's treatment is extensive. Apart from the physical therapy it involves use of mechanical devices such as mist tents and/or inhalators, regular intake of a variety of drugs and a special diet. Few if any other chronic diseases require this amount of different therapy on a daily basis.

The aim of the therapy differs for different groups of handicapped children. Children with cerebral palsy or with auditory or visual impairment need assistance to learn skills and to take part of social life. For the CF child, however the therapy is vital, and for the CF family there is often the feeling of despair and the feeling that however much treatment one gives, or whatever one does the child will not be better. Suddenly without warning, the child might get worse. In this respect the CF child can be compared to children with malignant diseases or immunopathies.

The physical nearness between mother and child involved in therapy and treatment for all groups of children is often perceived as positive when the child is young, but later on turns into something negative as the older child strives for independence. The close involvment often leads to overprotection from the mother and a very close mother-child unit is often found, sometimes expelling the father to the position of an outsider. The same situation has been found in families with asthmatic children (73), hemophilic children (2) and in families where a child suffers from Tay Sachs disease (53).

CF is an inherited disease which may lead to shame and guilt feelings in some parents as in the carriers of other inherited diseases, e.g. the mothers of hemophilic boys (83), and parents of children with certain kinds of mental retardation (80).

As the CF child grows up, he is faced with the problems of becoming independent. His very strong dependence upon his parents for his daily treatment makes it very difficult to move away from home. The CF boys are faced with the problems of a probable sterility and for CF girls a pregnancy may be perilous, as is also the case with diabetic girls.

As for all young adults with a chronic illness or

handicap it is very difficult to get an employment and the problem of how to be able to cope on their own and of how to be able to care for a family of their own is difficult to solve. The great variety and the difficulty of the problems faced by young persons with CF certainly qualifies them for this special investigation.

Earlier investigations

Handicapped children

The growing interest for comprehensive medical care in pediatrics has led to a number of studies where psychological, emotional and social aspects of chronic disorders in children have been investigated. The results can in many instances be generalized from one chronic illness to another. Several investigations have been made in this respect on boys with hemophilia and their parents (1, 2, 3, 14, 36, 84, 85) disclosing i.a. anxiety and feelings of helplessness and denial in the children, and anxiety, helplessness, sadness, guilt, anger and excessive overprotection of the ill child in the parents. The mothers of children with cardiac disease (34) often have a constant fear that the child will die and are thus often anxious, overindulgent and lax in discipline, while the child, who often suffers from severe anxiety, may respond with depression and withdrawal or by becoming angry and aggressive. Children with pulmonary tuberculosis (25) have been shown to have intense feelings of anxiety, marked feelings of inadequacy and preoccupation with thoughts about death.

Depression, strains on marital relationships, overprotection and difficulties with healthy siblings has been disclosed in families where a child has had to have a kidney transplantation (51) or is mentally retarded (11, 80, 101). In the latter families chronic mourning is often found among the parents, something which is also found in the families of children with malignant disease (20, 30, 75, 100). Concern by the mother as to her own role in handling the illness and her feelings of inability to provide proper and effective care is found among many mothers of children with rheumatic fever (35). A disturbed body image, obvious difficulties with their identification and signs of anxiety and aggression are frequent findings in children with diabetes mellitus (31). Coping behaviour, intense anxiety etc. has also been studied in physically ill children and their families in general (19, 35, 42, 77, 90, 97, 98, 99).

As in all patterns of human behaviour however, the discrepancies of the modes and successfullness of coping behaviour between the individual families in most of the cited studies are great. What destroys one family may strenghten another. Many children and parents adapt surprisingly well to their problems. The parent-child-family balance appears to be more influential than the nature of the specific disease or handicap.

Cystic Fibrosis

The recent advances in CF therapy has led to a longer life expectancy for the patients. Comprehensive studies of CF children and their families have been made, dealing with the impact of CF on family functioning (107, 114) and with the psychological implications for the children and their parents (4, 12, 15, 16, 24, 69, 71, 86, 89, 107, 111, 113, 114). These investigations have, with few exceptions, been made on relatively small numbers of CF children and, with one exception (16), only with patients from respective investigator's own clinic. The children have always been treated as a group, sometimes divided into subgroups according to age, but no consideration has in any of these studies been taken to the individual medical conditions of the children.

Marked anxiety, preoccupation with death and depressive trends among children with CF has been reported (12, 71, 86, 107). Tropauer (113), however, found a general absence of apparent depression, probably due to the fact that children rarely exhibit depression in the characteristic way of adults. This author also found that anxiety was experienced by many of his patients regarding the image of themselves in relation to their environment.

In a study by Lawler (71), clinical signs of depression together with depressed hostile feelings towards the child were found in the majority of mothers as was evidence of psychiatric and

psycho-somatic disorders in the fathers. Depression in both parents was found by McCollum and Gibson (86), and by Allan et al. (4). Discomfort of varying degrees when communicating with the CF child about his illness has been reported (12, 69 86, 114) as has difficulty for the parents in communicating with each other about other aspects of their child's illness than the routine practical treatment problems (12, 69 113 114). Feelings of social isolation and disturbances of sexual relationships among parents have been reported by Turk (114). Burton (16) and Lawler (71) found, often severe, marital strain among the parents due to CF In contrast to this are the observations of Allan (4) who found that the burden of raising a CF child had strengthened the relationship among 1/4 of the couples in his investigation. In the latter study it was also found that the mothers were physically healthier than the fathers although 20 % of the mothers suffered from severe migraine and tension headaches, or constant physical tiredness or exhaustion. Fifty percent of the mothers stated they suffered depression or "neuroses which required periodic or continous medical treatment.

The importance of the early mother-child relationship and the personality of the mother as a base for the child's future adaptation has been stressed by several authors (5 86, 90).

Tropauer (113) has found that the involvement of parents in the physical care of the child is extremely important in facilitating parental adaptation.

According to Kulczycki (69) one of the critical variables in the parents response to their child's illness is the age at diagnosis and the difficulties the parents have had in obtaining the diagnosis. It has been noted that there seems to be no relationship between the severity of the child's illness and the adaptation of the parents (69).

Meyerowitz and Kaplan (89) suggest that the presence of siblings who know the diagnosis is an additional source of stress to the parents.

The very real need of and dependence on a long term association with an interested, sympathetic physician has been stressed (11 69).

High average IQ s among children with CF have been reported by several authors (12, 16, 69 71 88). In spite of the fact that their school attendance, in main, was excellent, all but one of the children in Burton s material (16) were, however measurably retarded in basic school subjects. In another study (71), the majority of children were also underfunctioning. In Cytryn's study (23), however the majority of children were functioning effectively at school.

Beck et al. (8) very interestingly found that an unusual number of CF children in her study of 30 children suffered from visual-motor difficulties, and that, in the children so afflicted, there seemed to be a high correlation with early severe, respiratory illness.

Boyle et al. (12) found marital difficulties in all marriages between a CF patient and a healthy spouse despite varying styles of upbringing and behaviour This indicates that it is very difficult for a healthy spouse to cope with a chronically ill person, despite good intentions. None of the healthy spouses had any conception of what it was like to live in a household geared to complex treatment regimens and repeated crises.

Normal children

In the study of normal child development, Eriksson, Piaget and Sears (79) all share the conviction that whatever occurs during the early years of a child's life is basic to the child's later adjustment. According to Sears, the child's development depends on the dyadic interaction between its caring adults—usually its parents—and itself It is the quality of this interpersonal relationship, both attitudinal and physical, between parents and child, which is of utmost importance.

In the case of identification, Sears and Eriksson (79) also focus on the attitudes reflected by the parents as the most decisive variable. Identification can, as a process, be traced to the quality of mother-child relationship in the mother s efforts to provide gratifying experiences in infancy and conversely in the child's need for his mother

Child rearing depends upon finding a proper balance between providing too much and too little

in any one area. In the case of dependency proper development, according to Sears (79), depends upon furnishing an appropriate permissiveness as well as appropriate limits in order to foster gradually more and more independent actions and control.

The nursing person, usually the mother can, according to all three theories, instill in the child a basic sense of security only as deep as her own. This makes it important, in the case of all children, healthy as well as ill, to focus on not only the child but on the entire family.

Aim of the study

The primary goal of this investigation has been to disclose special characteristics among children with Cystic Fibrosis and their families and to focus on important consequences of the illness.

The main issues have been

1. to explore the quality and the magnitude of psychological problems that CF imposes on the child and its parents
2. to investigate how the CF child experiences and reacts to its illness
3. to assess if the CF child differs emotionally, intellectually or in visual-motor functioning from peers
4. to see how the parents adapt to their child's condition and cope with the problems
5. to assess the need of help and how it can be given

II. MATERIAL

When this study was designed (June 1971), 150 patients with a confirmed diagnosis of CF representing 140 families, were living in Sweden. Their ages ranged 3 months to 25 years (Diagram I).

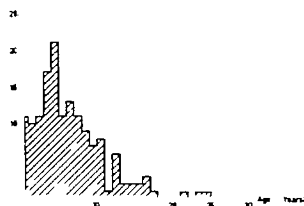


Diagram I. Age distribution of CF patients in Sweden 1971

Since every patient was registered centrally at the University Hospital of Uppsala, the total population of diagnosed CF patients in Sweden was known (63). The families were spread all over the country and with the exception of the largest cities, Stockholm and Gothenburg, there were great distance between them.

There were, in Sweden 1971 four CF-centers (Uppsala, Stockholm, Gothenburg and Lund), where the patients living in the nearest surroundings were treated. The majority of the children, however did not have any regular access to specialists and were treated by pediatricians at the local hospitals.

Fiftytwo children from 50 families were used in this study. Their ages ranged 4 years, 6 months to 15 years, 1 month. Random tables were used in order to get a representative sample from the whole country. Twentytwo preschool children (50 % boys and 50 % girls) and 30 school children (also 50 % boys and 50 % girls) were obtained in this manner. They represented 52 % of the children with CF in Sweden in this agegroup.

The mean number of living children in the CF families included in the study was 2,3 with the range 1—6. The CF child was the only child in 10 families. Six of the families in this investigation had 2 living children with CF. In 2 of these families both children were randomly included. Eight families had had a CF child, now deceased, prior to the one participating in this study.

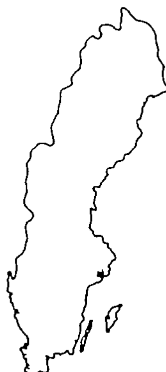


Fig. II. Geographical distribution of the CF families included in the study

III. METHODS

The methods chosen were

a. a medical evaluation of the children
b. an extensive interview with the mothers
c. a personality inventory (mothers)
d. psychological tests
d. a questionnaire for the teachers.

All interviews and testings were done by the author. They were completed on the same day in 41 families. In 9 families, including the two with 2 CF children, one or 2 further visits were required because of the length of the interview and tests.

The author has scored all tests. The Bender Gestalt test and the Human Figure Drawing test were dubble scored with an inter scorer reliability of .91 and .93 respectively.

a) Medical evaluation

The medical evaluation of all patients was made by Hans Kollberg, M.D. in the same way as earlier described (63) taking into consideration activity, heart-lung symptoms and nutrition (Table I).

Table II shows the severity of illness of the children in the material and a comparison to a reference material in Sweden, which includes nearly all known children 1970 (63). The medical condition of the children in relation to age is shown in Table III. The children are, according to their medical condition, divided into 5 groups: excellent condition, mild- moderate severe or very severe symptoms.

b) Interviews

The interviews were carried out between Aug. 1971 and Sept. 1974. Thirtynine mothers were interviewed in their homes, 10 mothers were seen at a camp for CF children and one mother in the home of a friend due to her fear that her CF boy might question her about the author's visit. A minimum of 4 hours and a maximum of 3 whole days was spent with each mother.

The inquiry form consisted of 102 questions but some of these had to be excluded from the account because of the volume of the investigation while others gave no further information. The complete questionnaire is given in Appendix I. The questions excluded in the account are marked with *).

The interview was divided into 3 parts: 1) the pre-diagnostic phase, defined as the interval between the parents' first suspicion of something being seriously wrong with the child and the diagnosis of CF; 2) the diagnostic phase and 3) the long term adaptive phase. As it was neither possible nor desirable to pose the questions in any given order one phase at a time was discussed. For practical presentation the answers were grouped according to the categories given in Appendix I.

c) The Eysenck Personality Inventory (EPI)

The EPI was administered to the mothers. This personality inventory is a self-rating instrument which measures the personality traits of Extroversion (E) and of Neuroticism (N) as these concepts have been deduced by Eysenck (27). The EPI also includes a Lie scale (L), which is intended to detect subjects who tend to present themselves in a favorable light. The EPI consists of 57 items and exists in 2 parallel forms, A and B. Twentyfour E items, 24 N-items and 9 L-items are included in each form. The B-form was used in this investigation.

The EPI was included as it was hypothesized that the mothers would show a high degree of neuroticism.

Table I. Medical evaluation of the children

	3 points	*2 points*	*1 point*
Activity	Plays all day. Does not rest during the day. Does not go to bed earlier than peers. Participates in gym at school. Runs upstairs.	Insufficient energy to play all day. Rests now and then, takes nap. Goes to bed early. Does not participate in gym or participates sometimes. Walks upstairs.	Tires easily, often rests when walking some 100 m. at a time. Looses breath easily, heart beating, may become cyanotic. Does not participate in gym. Can hardly walk upstairs.
Heart and lung symptoms	No continuous cough. Only short cough periods and clear sputum. Unfrequent colds.	Continuous, almost daily bad cough. Discoloured, viscous, foul-smelling sputum. Frequent colds.	Al ys coughs, cough may sound like whooping cough. Ugly olumnous sputum. Frequently has fe er and pneumonia. Often cyanotic.
Nutrition	Height and weight over 25 percentil. Normal bowels 1–3 times day. No abdominal pains. No prolapse of the rectum.	Height and weight between 3–25 percentil. Voluminous, loose, fatty, foulsmelling stools. Frequent abdominal pains. May have had rectal prolapse	Height and weight under 3 percentil. Stools that may invalidise the patient.

Table II. Medical condition related to severity of illness

Degree of illness	Reference material % n 122	No of children in investigation	Activity heart-lung symptoms and nutrition according to Table I.
Excellent condition	21	9	3-3-3 or 3-3
Mild symptoms	34	14	3-3-2, 3-3-1 3-2 3 3-2 2
Moderate symptoms	36	17	3-2 1 2 3-2, 2 2 3 2 2 2 1 2 1 3 3-1 3 1 3-3 3-1 2, 3-1 1 2 3-1 1 3-2, 1 3-1 1 2 3
Severe symptoms	7	9	2 1 2 2 1 1 1 1 2, 1-2 1 1 2 1 1 3
Very severe sympt.	2	3	1 1 1
	100	52	

Table III. Medical condition in relation to age

Age	*Condition* Excellent	Mild	Moderate	*Severe*	Very sev
under 5	4	1	2	1	1
5–7	4	4	4		2
7–9		3	4	4	
9–11		2	3	1	
11–13		1	2	3	
13–15	1	1	1		
over 15		2	1		
n =	9	14	17	9	3

d) Psychological tests

The following test battery was used

The Wechsler Intelligence Scale for Children *or*
The Leiter International Performance Scale
The Bender Visual-Motor Gestalt test
The Human Figure Drawing test

Intelligence scales

In order to get an intellectual cognitive assessment of the children, the Wechsler Intelligence Scale for Children (WISC) (*117*) was administered to the children above 6 years, 0 months of age. For children below this age the Leiter International Performance Scale was used (7).

The Bender Visual Motor Gestalt test

The Bender test occupies a unique position among major clinical diagnostic instruments as a brief test that is both projective and non-projective. It gives contributions to the evaluation of perceptual motor functioning, neurological impairment, expressive styles and maladjustment (56). It consists of 9 simple designs (App. III), each of which is presented one at a time to the subject for him to copy on a sheet of paper

The Bender Gestalt test was administered according to Bender (9). Complete scoring was done by 2 systems, according to Pascal & Suttell (94) and to Hutt (48). The interscorer reliability of this test has been calculated to .90 and .91 respectively (48, 93).

The Human Figure Drawing test (HFD)

A child's HFD shows both a basic structure and a certain mannerism which is peculiar to that particular child (67). The structure of a child's drawing is determined by his age and level of maturation, while the style of the drawing reflects those attitudes and concerns which are most important to him at that time (55).

The HFD test, as defined here, requires the child to draw "a whole person" in the presence of the examiner. The drawings are analyzed for signs of unconscious needs, conflicts and personality traits. Thirty "emotional indicators" have been used. They have been isolated by Koppitz (67) according to the following criteria.

1. They have clinical validity to differentiate between HFD:s of children with and without emotional problems.
2. They are unusual on the HFD:s of normal children and occur on less than 15 % of the HFD:s of children at a given age level.
3. They are not related to age or maturation.

The grading is straightforward and rarely ambiguous. *Earlier investigations have confirmed the* validity of a sign approach to personality when the HFD:s are scored according to Koppitz (43).

A contributing factor to the choice of the specific psychological tests (Bender and HFD) was that Kerstin Fällström had used these tests in her study of diabetic children where they were shown to give results (31). Thanks to a close collaboration with Kerstin Fällström it was possible to compare her results of diabetic and normal children with my own

e) Questionnaire to teachers

The teachers' questionnaire was mailed to 24 parents of school children who gave it to the teachers to complete. To have the parents give the teacher the questionnaire rather than mail it directly to the teacher was considered important in order to avoid that the parents feel that this contact was made "behind their backs". It would also help increase communication between parents and teachers.

The questionnaire had closed answers (App. II) and requested information about.

1. How the child copes with CF in school
2. The reactions of the CF child's peers to its illness
3. How the CF child adjusts to other children
4. The CF child's scholastic ability
5. The CF parents' contact with the teacher

All but two teachers answered the questionnaire. An additional letter was sent directly to these two teachers as the parents reported that

they had handed over the questionnaire. In spite of this no answers were obtained.

The questionnaire was not sent to 6 teachers whose CF pupils had passed away during the time between testing and questionnaire.

Statistical methods

Ordinary statistical methods were used for calculations of means, medians, standard deviations and percentiles. In testing for the significance of differences, the Chi-square test, the Mann Whitney U-test and the t test were used.

IV RESULTS

1 Interviews

a) The pre-diagnostic phase (Questions 1 2, 4 5 6 7 8, 9 10, 11 12, 14 and 17 in App. 1) n = 52

The pre-diagnostic phase is here defined as the interval between the parents first suspicion of something being seriously wrong with the child and the day of diagnosis of CF i.e. the day when the diagnosis first appears in the child's medical records.

Diagram II shows the duration of the pre diagnostic phase for each individual child. Fifteen of the children (30 %) were diagnosed within 3 months of the first awareness of something being wrong. Among these children were 8 who had

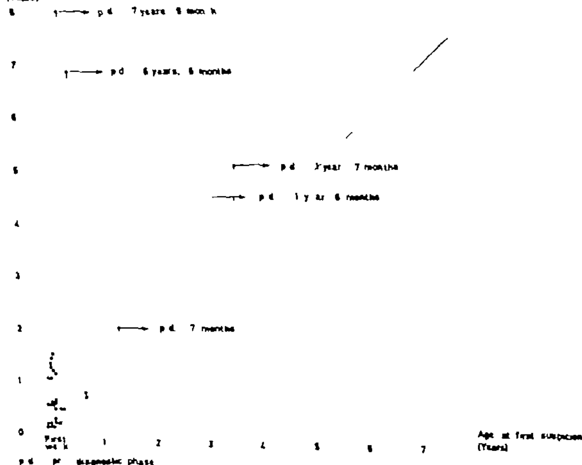


Diagram II. Duration of the pre-diagnostic phase.

elder siblings with known CF Only one child with an elder sibling with known CF had a longer pre diagnostic period—6 months.

For 18 children (35 %) more than one year (maximum 7 years, 9 months) was needed to obtain a correct diagnosis. Of these 18 children there were 15 who were the family s first child.

In more than half of the cases, the parents suspected that something was seriously wrong with their child already during the first month of life. Only in 4 families were the parents unaware that their child had a problem until after the first year of life.

For all mothers but 4 (2 of which received the correct diagnosis at once) the months or years before the child was diagnosed were characterized by a considerable and continuous distress. This was irrespective of whether the duration of the pre-diagnostic phase was short or long or of whether the child was hospitalized or not. For the parents who had already lost a CF child or who had an existing diagnosed CF child, the suspicion and dread that this child too would be stricken made the situation still worse.

The most frequently stated reason for first alarm was the baby s fatty frequent and foul smelling stools, general failure to thrive and/or feeding problems, vomiting or constant crying. This was a time spent seeking medical aid, and remarkable initiative was often shown by the parents in their struggle for a correct diagnosis. For the 36 children who were not retained at the hospital after the first visit to a doctor or at once after birth, endless and often frustrating visits to physicians and hospitals became routine, the parents being certain that their child had a problem. Often the mothers blamed themselves for their child's failure to thrive. Four mothers, for example, all from rural areas or small towns, stated that the additional burden of family's, friends and neighbours (real or imagined) contempt of them because the child looked undernourished and un well and their firm belief that others thought them unfit to take care of their child, made the situation even more difficult to bear The parents of 21 children went "doctor shopping seeking help of between 2 and 9 different doctors, several also of homoepathists.

Incorrect diagnoses were often made causing additional stress as the prescribed treatment failed to be effective. Celiac disease, allergy whooping cough and intestinal tumors were some of the diagnoses given. One half of the total group of mothers (including some who had their children in the hospital for observation) felt that they found no understanding or concern for their distress from the physicians. They felt they were treated like fussy hypochondriacs, constantly being told that nothing was wrong with their child, that the child was prone to colds, that it was not always easy to have a child and that they should have thought of this before they had one, or that the child would outgrow his troubles. One mother whose child had up to 20 stools a day was told that "if there is input, there is bound to be output Several mothers, specially the ones who had had no child before the CF child, eventually started believing that they were the ones who were wrong and felt badly about "disturbing" the doctor (again). A large number of mothers suffered from lack of sleep on account of constant worry or of the baby s incessant crying and many had severe depressions resulting in hospitalization in 2 cases. One mother woke up screaming nearly every night. As one mother put it "I didn't enjoy my child a single minute."

b) The diagnostic phase (Questions 19 20, 21 24 25 and 27 in App. I) n = 50 families

In 32 % of the families, the father was not present when the diagnosis was given.

The first reaction to the confrontation with CF was either shock (58 %), relief (23 %) or no special reaction (19 %).

The types of reactions have been correlated to a number of special parameters. There were no significant correlations with the duration of the pre-diagnostic phase, the medical condition of the child, the amount of information given or the manner in which the information was supplied. The fact that a diagnosis had at last been made, that a treatment plan could be started and the assurance that it was not an illness that the parents perceived as a more serious one, such as cancer was the main reason for relief. Lack of

earlier frightening information about the disease was related to no special reaction and even, to a certain degree, to relief

Fortytwo percent of the parents perceived the information given them during the diagnostic period as adequate, while 58 % perceived it as inadequate. The latter group felt they were given insufficient information or no information at all.

Fiftytwo percent of the parents felt that the diagnosis had been given them in a satisfactory manner even if they in some cases did not receive adequate information. Among these parents were those who had an earlier CF child and who expected the diagnosis. The remaining 48 % of the parents however were given the diagnosis in a manner they experienced as negative or very negative.

It is in this context important to point out that it is certainly not possible to determine how much of the parents view of the manner in which the diagnosis was given or the amount of information supplied during the period of diagnosis that is a function of the parents own perception and how much is a function of the actual actions of the physician (see discussion).

The criteria for adequate information were

1) satisfaction with the amount of information supplied and the manner in which it was given,
2) a positive feeling that the physician took time with the parents and explained the facts in a straightforward and honest but sympathetic manner without depriving the parents of all hope,
3) the physician had made sure the parents had understood the information given and the parents felt that they were given all the knowledge the doctor himself possessed.

The way that inadequate information was given in could be defined in 4 groups

1) the only explanation of CF given was simply that very little was known about the disease. (This was given to about 20 % of the parents and their own feeling was that they could accept this explanation.)
2) scant, reassuring but unconvincing information, often of only one detail of CF (This was given to 11 % of the parents and they were negative to the information.)
3) An, according to the mothers, frank explanation that their child was going to die and very little further information. (This was given to 14 % of the couples and these were extremely negative to the information and felt that it was given in a brutal and unsympathetic manner.)
4) No information at all (13 %).

Some of the negative experiences can best be illustrated by examples stated by the mothers. One stated that she was simply told that her child had a mysterious illness called Cystic Fibrosis and whatever she did the outcome was death. She was told to come back in a couple of days so that the doctor would have time to find out some more about the disease. Another mother who was pregnant with her second child when her first boy got the diagnosis, met the doctor in a corridor and was told that the diagnosis had been made. Her boy had CF and was expected to live at the longest another year and the child she bore was most likely to have the same disease. The doctor did not have time for further explanations at that time. A third mother was told on the telephone that a diagnosis had been made, that the illness was fatal and death was to be expected within one year. These examples were from the years 1969—1971. It is here to be noted that parents were not negative if they were told that the illness was fatal by a doctor who they otherwise perceived as sympathetic and who simultaneously gave other information about the disease (adequate group).

Thirteen percent of the couples received no help whatsoever. Pills were prescribed in all of these cases.

A large group of parents who received inadequate information neither were given nor asked for more information during later contacts. Many believed they had been told everything that was known and others stated that they didn't know what questions to ask. Since many of these children were seen by new doctors at every visit to the clinic, the doctors might have taken for granted that preceding doctors had given adequate information. Some parents did ask

questions but received no further enlightment. A small number did not dare ask out of respect for the doctor. Examples from mothers: "It was so awful, I didn't know if CF hurt or not." "I didn't know where CF was located or whether it hurt, only the name."

As many as 29 % of all parents in the entire group first learned, or learned more than one detail or other about what was really wrong with their child when RfCF (Riksföreningen för *Cystisk Fibros* = the Swedish Association for Cystic Fibrosis) was founded 1969 and a lecture on CF was given. Another 6 %, not members of RfCF, first learned when the author visited their homes on account of this investigation.

e. **Long-term adaptive phase**

Genetic information and counselling (Questions 44–46, 47–48 and 49 in App. I) n = 50 couples

Twentyone of the couples had received genetic counselling and correct information about how CF is inherited before further children were conceived. To 11 of these couples, 14 further children were born, 2 of whom had CF. When these parents were counselled

4 couples had been encouraged to have another child — 4 children born

5 couples had been given a neutral information — 3 children born

12 couples had been definitely advised against further children — 7 children born.

These parents gave different reasons for having further children. The most commonly cited reason was that "it was worth taking the chance". Four couples, however, had misunderstood the information they had been given. They believed that after a CF child was born in the family, the following 3 children would be healthy after which another CF child would be born.

Twentynine couples were given incorrect information about how CF is inherited, no information or information that came too late for the parents to prevent another pregnancy. To 20 of these couples 27 further children were born before correct information was received, 12 of which had CF. Eight of these families had received no information, 5 had received incorrect information and in 7 families the first CF child was not yet diagnosed. (See fig. III.)

Current contact with physicians (Questions 34, 35 and 36 in App. I) n = 52 children in 50 families

The parents of the 28 (54 %) children who were treated by CF experts at regional hospitals were all satisfied with the doctor who treated their child. Of the others, 13 were satisfied, 4 were neutral, while 7 were dissatisfied.

The reason that the mothers were satisfied related mainly to the personality of the doctor (21 mothers). Appreciation of such things as personal interest for not only the child but for the entire family, of being told that they could call the doctor whenever they felt the need, of being told where the physician could be reached when away or who could be reached instead were cited. Judgements of the doctor as being "wonderful" and "a real friend" were often made.

Seven mothers gave the doctor's knowledge about CF and his ability to treat their child as the most important motive for their satisfaction. All mothers belonging to the neutral group stated that their doctor was competent but impersonal.

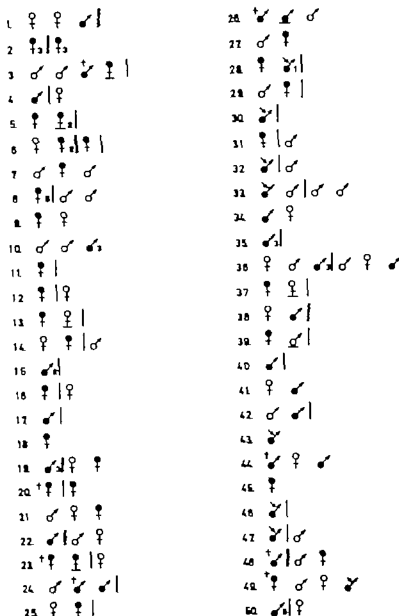
The parents in the dissatisfied group had no steady doctor. Instead their children were seen by different physicians who the mothers felt were incompetent.

The parents' mutual relationship (Question 33 in App. I) n = 49 couples

Two families had 2 children included in the study; one mother was widowed before the child was born.

Nineteen couples felt that their mutual relationship changed in a positive direction, thus improving and becoming richer with the problem of having and rearing a CF child. These parents all felt that they now, after the child had been born, had something important to fight for together and that this one problem was great enough to overshadow other problems that might arise in the marriage.

Thirteen couples felt that the strain of their



♂ Healthy boy

♀ Healthy girl

CF boy

CF girl

Deceased CF sib.

Healthy boy born before diagnosis of elder CF sib.

CF boy born befor diagnosis of elder CF sib

CF girl incl. in present study

CF girl not included in study moder to med. cond.

Correct genetic information

Incorrect genetic information

Medical condition

1. Ex Heal
2. Mild
3. Moderat
4. Sever
5. Very severe

Fig. III. Children in the CF-families.

child's illness had weakened their marital relationship. Reasons given for this were especially that the CF child took all the mother's time, energy and interest away from the rest of the family and the lack of help in the treatment from the father. Three of the couples in this group were divorced shortly after their child had got the diagnosis of CF which, (according to the mother) was due to the strain on the marriage that the sick child caused.

Seventeen couples felt that no change in the quality of their marriage had taken place.

The pattern of change or conformity was not related to the severity of the illness of the child.

The Parents' mutual communication about CF (Questions 87 and 93 in App. I) n = 45 couples

Two couples had 2 CF children included in the study, one mother was widowed before the child was born, 4 couples were divorced and had no contact with each other.

Among the 36 couples whose relationship, according to the mothers, was unchanged or better, nearly all gave one another mutual support and were able to communicate freely with one another about all aspects of CF. Several of these mothers spontaneously claimed that they and their husband found their common problem with CF so important, almost "holy", that they never quarreled or argued amout anything any more.

Fourteen (31 %) of the couples had great difficulties in their mutual communication about their child's illness. Remarks and questions about CF were made now and then in these families, but the subject was never mentioned other than rarely and then causually. The mothers in 4 of these couples stated that they and their husbands had no need or wish to discuss CF with each other. They thought, however, that they could communicate on the subject if they should want to. In another family the parents discussed their child's illness to a certain extent but the mother kept serious aspects of the illness from her husband as she wanted to spare him a distress which she thought he would have difficulty to bear. The remaining 9 mothers all expressed a very definite wish to be able to communicate on this, for them very vital subject with their husbands, but they never received any response when the subject was brought up. This lack of response was, according to the mothers, due to pure disinterest on the part of the father in 4 families and due to the sensitivity of the subject in 5 families. The last mentioned 10 mothers all showed an enormous need to speak about CF with the author. One mother, when the author left her home, said it had been one of the happiest days of her life because she had for the first time been allowed to and dared to speak about what was always on her mind.

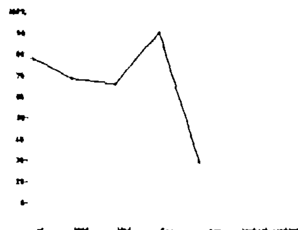


Diagram III Capability of the couples to discuss CF in relation to childs degree of illness.

Treatment (Questions 58, 59, 60, 66, 67, 68 and 69 in App. I) n = 52 children

By treatment is here meant the time the parents spent each day treating their child actively—i.e. with inhalations and physical therapy. Time spent cleaning and caring for apparatus (averageing 37 minutes a day), administering drugs and preparing special diets (averageing 10 minutes a day), visit to doctors etc. are not included.

Diagram IV gives the time of treatment when the children are "well" and diagram V when ill or infected. Diagram VI is a graphical drawing of the mean times. All treatment times are related to severity of illness.

Five children, 3 with a mild condition and 2

Med. cond	A	B	C	D	E	F	G	M
Exc	1	3	2	3				45 min
Mild	4	7	3					18 min.
Mod	2	4	2	8	1			1 hours 2 min
Sev.			3	3	3			1 hours 45 min
V sev				1	2			2 hours 30 min
								Time spent treating child

Diagram IV Time alloted to treatment when child not infected

Med. cond	A	B	C	D	E	F	G	M
Exc		1	4	2			2	2 hou s 58 min.
Mild	4	3	5	1		1		47 min.
Mod.	2	2	5	2	2		4	3 hours 8 min
Sev			1	3	2		2	3 hours 54 min.
V sev				1			2	7 hours 50 min.

Diagram V Time alloted to treatment when child ill or infected.

= one boy always at hospital when ill or infected A = no treatment B = 1–30 min/day C = 31–60 min/day D = 1–2 hours/day E = 2–4 hours/day F = 4–6 hours/day G = more than 10 hours/day

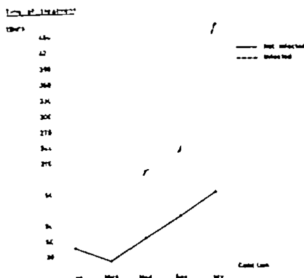


Diagram VI. Graphical drawing of treatment times.

[illegible]	[illegible]	[illegible]	[illegible]
[illegible]		2	4
[illegible]		1	4
[illegible]	7	1	7
[illegible]			6

Diagram VII The parent s experience of treatment.

with a moderate condition were never given any treatment irrespective of whether they were infected or not. Among these, 2 of the children with a mild condition had no symptoms from the lungs while the third had such symptoms. The mother of the third child had never been informed that there was such a thing as treatment. The 2 children with a moderate condition had made such a fuss each time treatment was to be given, that the parents didn t bother with it any more. Two children, one in excellent condition and the other with mild symptoms, received no treatment when not infected but some treatment when ill. Another boy with mild symptoms received 45 minutes of treat ment when not infected but none when ill as the parents then didn't have the heart to "bother" him. This was also the case with 2 other children who received some, but far less, treatment when they were ill than when they were not. Two children gave themselves what little therapy they got.

The 2 mothers of children in excellent condition who treated their children 1–2 hours/day when well and more than 10 hours/day when infected or ill showed a very high degree of neurotisism on the Eysenck Personality Inventory No other relations were found between length of treatment and the mothers scores on this scale.

The children in excellent condition received an average of 27 minutes more treatment per day than the children in mild condition when not ill or infected, and an average of as much as 124 minutes more treatment a day than the mild group when infected or ill. The divergence in amount of time spent with treatment of children in excellent and moderate condition resp. is, on the other hand, not very great.

Diagram VII shows how the parents experienced the administration of therapy in relation to the length of time per day the treatment was given. No significant difference was found in relation to the child's medical condition. Nearly all children tended to experience treatment in the same way as their mothers.

The daily treatment of the children was in the great majority of cases given by the mothers. Only in 7 families did the father give daily help. In 13 families the fathers helped 1–4 times a month while half of the mothers never received any help whatsoever Three of the fathers had never watched their wives give their child therapy although they as a rule were at home when it was given.

Diagram VIII shows the extent the fathers help with the treatment of their children in relation to the time spent with treatment each day

Six families in this study had more than one living CF child. In these families with a double burden of treatment, 2 fathers gave daily help one helped once a week, one somewhat less than once a month and 2 never

The child's experience of his illness according to the mother Parent-child communication. (Questions 71 74 75 76, 77 78 and 79 in App. I) n = 52 children

[illegible]				
[illegible]				1
[illegible]	1	1	3	1
[illegible]	4	4	5	
[illegible]	5	5	5	4

Diagram VIII. Father's participation in the physical treatment.

The mothers were asked how they thought the CF child coped with his illness whether it was not yet aware of having CF related in a natural way to it, suffered to some degree or suffered very much.

Diagrams IX and X show the answers in relation to the medical condition of the child in the 2 groups pre-school and schoolage children.

CF had in one way or another been discussed with 27 of the children in this study before they reached school age, and among these with 18 children before they reached 4 years of age. The child had either started asking questions or the parents had brought up the subject. No relation to the child's medical condition was found. Nine children who were under 7 years of age at the time of this investigation had not had their illness discussed with them.

Nine children, whose parents had not brought up the question of CF before the child reached schoolage, asked their first questions about their illness during the first school years. Among these was one child with a severe medical condition. Two other children were 11 years old when they asked their first questions, (one with a severe medical condition, the other in excellent condition) while one was 13 years of age (mild condition).

Four boys (2 in a moderate, 10 and 15 years old resp. and 2 in severe condition nearly 13 years old) had never brought up the question of their ill-

Relation	Exc	Mild	Mod	Se	V. se	N
Not conscious	3	3	2			8
Natural	3	2	3	1	1	10
Suffers some	1		1		1	3
Suffers much					1	1

Med. cond.

Diagram IX. Pre school childrens relation to their illness.

Relation	Exc	Mild	Mod	Se	V. se	N
Not conscious			1			1
Natural	1	7	3	2		13
Suffers some	1	2	5	1		9
Suffers much			2	5		7

Med. cond.

Diagram X. School childrens relation to their illness.

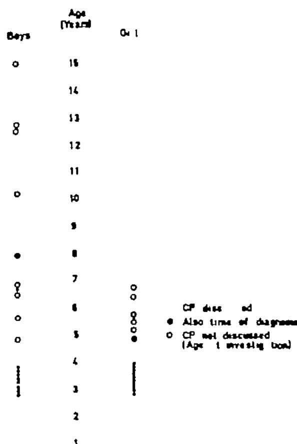


Diagram XI. Age of child when CF first discussed.

ness with their parents and their parents had never discussed it with them in any way. When these mothers were asked how they thought their boy coped with his illness one mother stated that she thought her son suffered somewhat and was embarrassed, 2 mothers thought their son suffered very much, while the fourth mother stated she didn't believe her son knew he was sick, this in spite of the fact that he had had an elder brother with CF had physical therapy regularly and ate several different kinds of drugs each day. None of these mothers believed it proper to bring up the subject of CF with their sons unless the boy took the initiative himself. Three of these 4 boys died within one year after the interviews. It would appear as if these mothers had remained in the second stage of crisis as described by Hill (45b) and by Cullberg (22).

Diagram XI shows the age when CF was first discussed with each individual child. Boys and girls are shown separately in this diagram.

Thirteen children had never asked any questions.

Thirtytwo of the mothers felt that they could answer their child's questions concerning CF in a satisfactory manner related to the child's age, and could cope with their own feelings when questions were brought up. The majority of these mothers tended to answer their child's questions truthfully but with certain paraphrases in order not to frighten their child. Seven mothers felt very upset when asked about the illness and had difficulties answering their child's questions. These children s medical condition ranged from moderate to very severe and the mothers either gave avoiding answers (5 cases) or very honest answers (2 cases) to their children s questions.

Table IV. Mothers' answers to their childrens questions about CF

n = 52 children		Age: 4 – 7 n = 22	7 – 10 n = 17	over 10 n = 13	Total
Can give satisfactory answers	Yes	13	12	7	32
	No	1	4	2	7
	No questions	8	1	4	13
Answer given are	Very honest	10	10	4	24
	Honest but paraphrased	4	3	3	10
	Avoiding		3	2	5
	No question	8	1	4	13

Mother's rating					
Leader		1	6		1
Forward			1		
Average		9	17		
Lonely	1	9		1	
Isolated	2				
	Isol.	Lonl.	Ave.	Forw.	Lead. Author's rating

Status: Excellent

	isol	lonl	ave.	forw.	lead.
Leader			2		
Forward				3	
Average			3		
Lonely		Y			
Isolated	/				

Mild

	isol.	lonl.	ave.	forw.	lead.
Leader			1		1
Forward				Y	
Average			9		
Lonely		Y			
Isolated		1			

Moderate

	isol.	lonl.	ave.	forw.	lead.
Leader		1	2		/
Forward			1	/	
Average		2	2		
Lonely		5		1	
Isolated	1				

Severe

	isol.	lonl.	ave.	forw.	lead.
Leader			1		/
Forward					
Average		5	2		
Lonely					
Isolated	1				

Very severe

	isol.	lonl.	ave.	forw.	lead.
Leader					
Forward					
Average		1	/		
Lonely	1	1			
Isolated					

Diagram XII. The childs position among peers as rated by the mother and the author

The child's social position among peers as rated by the child's mother and the author (Question 81 in App. 1)

The child's mother and the author individually rated the child's position among peers according to the following scale:

a) leader
b) somewhat more "forward" than average
c) average
d) somewhat lonelier than average
e) isolated
f) picked upon by everyone (Sw hack kyckling")

The teachers of 22 of the schoolage children rated the children according to the same scale. Eleven of the teachers rated the child's social position among peers as more favourable than did

both the mother and the author The ratings of the 3 judges coincided in 5 cases while the teacher s judgement was in accord with either the mother s (3) or the author s (3) ratings for the remaining cases.

Level of apsiration (Questions 54 55 56 and 57 in App. I) n = 49

The mothers of 3 children, 2 rated as severe, one as very severe, were not asked this question

In order to try to assess the parents level of aspiration for their child and to see how realistic these aspirations seemed to be, the mothers were asked to try to judge how they thought CF would interfere with their child's future possibilities 1 physically 2. socially 3 economically and 4 professionally

These thoughts for the future of one s child is not a thing that can easily be rated on a scale. They are a projection of hopes and of thoughts and feelings that one dares have, and of fears that are repressed. This question was regarded as so difficult for the mothers, that, in order to make it more acceptable and possible to answer a 100 point scale was given in contrast to the other scales in this study It was thought that parents may feel that they condemn their child if they place him or her on a lower scale unit than would be necessary if they had a larger variety of scale steps to choose from. This supposition was probably correct as virtually no mother used the scale under 50"

The following clarifications were made·

Physically

100 = CF does not in any way interfere with physical activities

0 = CF inhibits all physical activity Chair or bedbound.

Socially

100 = CF in no way an obstacle for making and keeping friends, of marrying or for being able to participate in social activities such as parties, staying overnight with friends etc.

0 = Total isolated

Economically

100 = Totally selfsupporting

0 = Totally dependent

Professionally

100 = CF places no restriction on choice of profession

0 = No possibility to find or accept a job because of CF

Note that "100" on this scale is not to be ranked as the medical condition of "excellent The point of "100" is unrealistic for all patients with CF except for the judgement economically"

Mothers of children in excellent condition or with only mild symptoms wished to identify their children more or less with normal healthy peers, except for profession where a fear of impair ment already was noticeable. A definite fall in all parameters was found when the children started to have moderate symptoms, but no further fall was seen for children in more severe medical condition on the contrary the mothers seemed to compensate for the more severe symptoms with a hope of better social possibilities. (See Diagram XIII)

Healthy siblings (Questions 94 and 95 in App. I) n = 37 families

Problems with healthy siblings due to having a CF child in the family were reported by the mothers in 11 of the 37 families (30 %) who in addition to one or 2 CF children had healthy offspring.

The age of the "problem siblings ranged between 3 and 23 years, 8 were younger and 6 older than the CF child. Three families had 2 problem siblings. Eight siblings were boys, 6 were girls.

By far the most often cited cause of problem was jealousy of the special care and attention the CF sibling received. The jealousy resulted in a variety of symptoms from incessant craving for attention, contraryness, egoism and excessive reservation to grave contact problems with peers, obesitas and school problems.

The mothers in 7 of the above mentioned families saw their helathy childrens jealousy as fully justified, confessing that they had very little

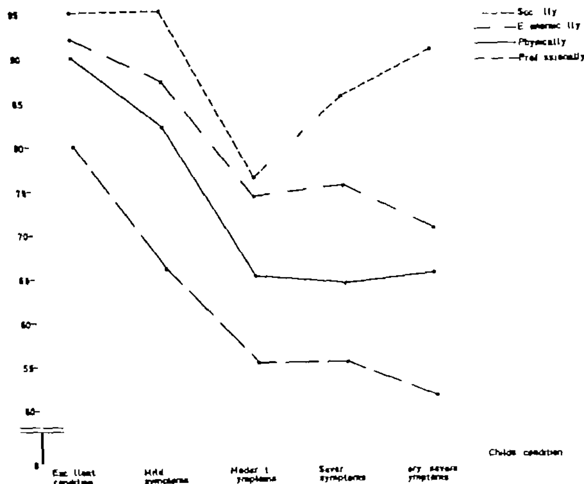


Diagram XIII The mothers level of aspiration for their child

time and energy left for these childrens needs. The remaining 4 mothers, all with CF children with an excellent or mild medical condition, saw the jealousy as unjustified as they felt all their children got the same amount of care, love and attention. Another 7 mothers said they had a permanent bad conscience because they had so little time for the healthy siblings, although there were, as yet, no problems. Contrasting to these mothers were 4 others who felt that the healthy siblings took so much time that there wasn't enough left for proper care of the CF child.

Mothers work (Question 99 in App. I)
n = 50. Two families had 2 CF children included in the study

Six mothers (7 CF children) had fulltime employment, 10 mothers had part time jobs and 34 mothers had no work outside the home. The CF children of the employed mothers were mainly in excellent or mild condition. Four were, however in moderate and 2 in severe medical condition. The treatment of the CF children of these mothers was arranged in various ways. In the

families where the mothers were full time employed, two children received no treatment, the mothers of 3 children worked in the same house that the family lived in and 2 were cared for by their maternal grandmother when not in school or ill. These latter 2 childrens parents were divorced. Nearly all mothers with part time jobs were able to stay at home when necessary

Ten mothers who now had no work outside the home were working prior to the diagnosis.

Twelve of the unemployed mothers resented very much to have to stay at home and felt very bitter because the care and treatment of the CF child prevented them from working outside the home. The feelings of these mothers are understandable but unfortunate as the child has a greater probability for healthy development if the mother does not yearn for another station in life (79). Another 6 mothers stated they would definitely have worked outside the home if they had not had a CF child, but they felt no bitterness.

The remaining 14 mothers stated they would have liked to be housewives regardless of whether the child had been ill or not. No correlation was found between the mother's level of education versus employment/nonemployment or versus feelings of bitterness.

Isolation and overprotection (Questions 96 and 97 in App. I) n = 50 families

Nearly half of the mothers in this study whose children represented the whole range from excellent to very severe medical condition, very definitely felt isolated because of CF and several stated that the whole family was isolated. Six of these mothers had 2 living CF children (while 4 had had further CF children). The reason for isolation most frequently given was, among the mothers with 2 ill children, the amount of time and energy needed for treatment. This reason was also given by several mothers with one CF child even if the risk for infections was more frequently given here. Other common causes of isolation were the impossibility to plan more than a day ahead, the difficulty of finding someone who dared look after the CF child and the anxiety to give the responsibility to someone else even for a couple of hours.

Parents of CF children had a tendency to yield to their children in a way they do not think they would have had if the child had been healthy. Seventyfive percent of the parents felt that they let their children have their own way in material as well as in other matters, often at the cost of their healthy siblings, to a degree they considered not quite good for the child. The parents justified their behaviour by wanting to compensate for everything the CF child had to go through. This problem included refusing to set limits on the child's behaviour as well as infantilizing the child by doing everything for him. No mother in this study felt that her child was overprotected—only that neccessary precautions were taken. Overprotection was, however very obvious in a great many of the families. Thus one 8 year old boy (see case 4) with a severe medical condition, who was quite capable of doing things for himself and who could even play football for reasonably long periods at a time, was dressed in the morning and undressed in the evening and often even fed by his mother. A girl, 12 years old, also in a severe medical condition, was able to jump rope and play tag with peers when her mother was not near. When her mother appeared, this girl sank to the ground and in a febble voice asked to be carried. Other children in various medical conditions were never allowed into a shop, bus or theatre. One boy was paid one crown every time he ran upstairs which was no real effort for him.

Nocturnal enuresis and sleeping difficulties (Questions 83 and 84 in App. I)
n = 30 school children (enuresis) and 52 children (sleeping difficulties)

Nine of the 30 school children (30 %) (average age: 10 years, 5 months) suffered from nocturnal enuresis—6 were wetting their beds every night, 2 once or twice a week and one at the slightest anxiety. Seven of the children had a moderate or severe medical condition. Five were boys and 4 were girls. No correlation was found between enuresis and contact with peers or between

enuresis and number of emotional indicators on the child's Human Figure drawing (67). The Eysenck Personality Inventory however (27), showed a very high degree of neuroticism in 4 of the enuretic school childrens mothers. Two further mothers showed a relatively high degree of neuroticism while the remaining 3 mothers had grades within normal limits.

Fourteen of all 52 children (27 %) in the study suffered from sleeping difficulties to such an extent that the parents experienced it as a problem. No correlation was to be found to the medical condition of the child or to the mother's grade on the EPI.

2. Questionnaire to teachers

The teacher's assessment of the child at school n = 22

Half of the CF children were, in the opinion of the teacher not physically inferior to their peers in any way—9 were considered to have the same amount of strength and endurance and 2 to have more strength and endurance than their peers. The other half however were considered weaker or much weaker than their peers and did not have the strength to compete in games etc. on equal or nearly equal terms. Without exception, these children were thought to do their best in games and competitions and their peers accepted them as they were and took their handicap into consideration in a very natural way.

Eleven children had a higher or very much higher rate of absence from school than what was normal in that class, 7 had about normal rate while 4 had a lower rate.

Only 2 teachers considered their pupils over protected by their parents. The mother of one of these pupils (severe medical condition) had never spoken to the teacher about her daughter's illness, and the teacher had only very scant information about CF from the school nurse. This mother had much less contact with the teacher than had the mothers of the girl's classmates. The mother of the second child took the initiative to contact the teacher much more often than other parents in that class. Among the remaining CF mothers, 3 had never spoken in person to the child's teacher about CF one had less contact than normal with the teacher 11 had normal contact while 5 had more contact than normal.

Four children constantly demanded the attention of the teacher and 3 of these also from their classmates. These are included in a group of 7 children who sometimes spoke about their illness to their teacher and peers, while the remaining 15 children never mentioned it.

No child ever blamed various difficulties in the school situation on CF but the mother of one boy blamed the boy's aggressiveness and bad behaviour solely on her son's illness. This and a second boy made "use" of their illness by for example pretending to be tired, when there was something they did not want to do.

Eight of the children were embarrassed by their cough in school and often tried to restrain from coughing. Their medical condition ranged from mild to severe, with the healthier children only coughing now and then, the more severely ill considerably more often. No teacher mentioned that their CF pupil was embarrassed to use the toilet in school. However 8 of the mothers stated that their children were embarrassed over their foulsmelling stools to such a degree as to constitute a school problem. Most of these children refused to have bowel movements in school. Five pupils were unhappy to eat drugs in the presence of others in school. Two of these children were given the opportunity to eat their pills in secret and 2 others preferred to go home for lunch. Four other children, 2 of whom were fetched by car by their mothers, also went home for lunch each day.

Eight of the pupils had reading and writing difficulties and received special help for this. Among these 8 children, 3 had difficulties also in other subjects.

3. The Wechsler Intelligence Scale for Children

n = 39 children above the age of 6 years, 0 months

The WISC test is divided into a verbal part and a performance part. Each of these parts are in turn divided into 5 subtests. A whole-scale IQ a verbal

IQ and a performance IQ can be calculated, as can Stanine scores (1–9) for the 3 IQ s.

The results of the whole scale yielded a mean IQ of 95 6. The range of IQ s was from 70 to over 127 with 4 children having IQ s below 85 Three children were in the superior range (IQ s of 120 and above), 5 were bright normal (110–120), 27 were average (90–110) while 5 were low average (85–90).

The mean IQ of the children on the verbal tests was 98.2 (boys 99.5 and girls 96.8) and on the performance tests 96.3 (boys 98.4 and girls 94 1). Transformed into Stanine scales all means for the whole test, the verbal tests and the performance tests were 4 7

Nothing extraordinary was found when studying the total results of the 2 different parts of the test as wholes. On the performance subtest Object Assembly however 16 children or 41 % scored a Stanine of 3 or below (all but one with average or high average whole scale IQ s) in relation to 9 children or 23 % which is the expected number This difference is, however not significant ($x^2 = 0.20 > p > 0.10$). Nine of these children also had low Bender scores (scored according to Koppitz (66)). However 2 children with superior Stanine scores on the "Object Assembly test also scored low on their Benders.

No proof of superior verbal talents were found in this study the mean Stanine score for the whole group on the subtest "Vocabulary" being 5 4

4. The Leiter International Performance Scale

n = 13 children under 6 years, 0 months of age

The Leiter test is a non-verbal intelligence test for children from 2 years, 6 months to 7 years of age. It has no time limit. The results are given in Stanine values.

The mean Stanine results of the children was 4 6 (boys 4 4 and girls 4.8) with the range 1–8. Both extremes were boys.

5. The Bender Visual Motor Gestalt Test

n = 33 children above the age of 7

The Bender test consists of 9 simple designs (App. III) each of which is presented to the subject one at a time for him to copy on a sheet of paper When scoring according to Pascal & Suttell (94) each scorable deviation (item) is numbered, named and weighed and a systematic method of accumulating scores by items, design totals and total for the test is provided. (Examples of scorable deviations is given in App. III).

Mean values (weighed scores) for 20 Bender items, scored according to Pascal & Suttell for measuring perceptual-motor deviations are given in Table V They are compared to the results of diabetic and control children 7–12 years old earlier reported by Fällström (31).

Individual scores for the diabetic and control children were not available for this test why testing of significant differences between these groups and the CF group was not possible. However all differences between the diabetic group and the control group, with the exception of Workover Design I, are significant ($p<0.05$) why the differences on all items except Distortion–Design III, Workover – Designs VI and VIII and Rotation – Design VIII also must be significant on at least this level of significance between CF and

Table V Mean values for certain Bender items (Pascal & Suttell) in CF children, diabetic children and controls

		CF	Diab	Control
Item				
Design I	Work over	94	(0.27	17)
Design II	Work over	44	.20	.01
Design III	Asymmetry	1.32	.27	.06
	Distortio	.50	76	.05
	Work over	1 18	.43	00
Design IV	Asymmetry	1 41	46	.01
	Distortion	.50	45	.00
Design V	Asymmetry	1.23	.34	.07
	Rotation	.96	.38	.00
	Distortio	72	.24	.00
	Work over	.88	.34	.09
Design VI	Asymmetry	2.52	43	.05
	Distortion	72	.57	.09
	Work over	.06	.81	.00
Design VII	Rotation	1 76	.49	.00
	Distortion	2.24	30	.02
Design VIII	Rotatio	.50	.84	.02
	Distortion	.96	.89	.02
	Work over	.06	.53	.08
No order		3.28	1.36	.09

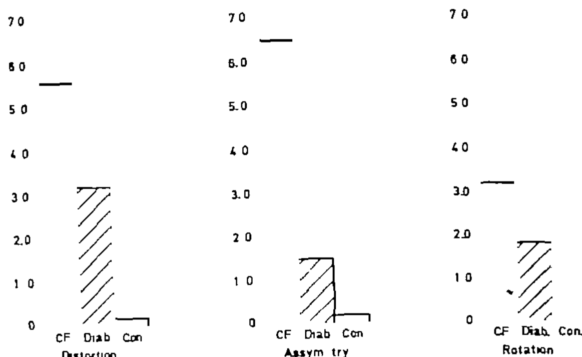


Diagram XIV Deviations according to P & S depending on organic changes among CF diabetic and control children.

control children. Very striking differences between CF and diabetic children are also obvious on many of the items.

Both the diabetic and the CF groups gave more abnormal responses on all items listed above than did the control group. The CF group however had far more abnormal responses than did the diabetic group on 16 out of the 20 items. All CF children had abnormal responses compared to 33 of 59 diabetic children and 3 out of 59 controls.

Considering all 105 items, all CF children, 45 of 59 diabetic children and 11 out of 59 control children presented one or more deviating responses.

According to Pascal & Suttell, the Bender test measures 2 kinds of deviations, one kind resulting from psychogenic illness and one kind from organic causes. Three items, distortion "assymetry and rotation are especially sensitive to brain damage. Diagram XIV shows the mean added frequency on all designs of these 3 items in CF diabetic and control children.

The Bender test has also been scored according to Hutt (48). (Examples of the scorable deviations are given in App. III.) This adaptation of the test is an attempt to use the procedures as a projective device (21 31), in addition to its capacity to detect perceptual-motor disturbances and discover cases of brain-damage not readily discoverable by routine neurologic diagnostic procedures. According to Hutt, high scoring on "change in size and angulation" perceptual rotation" and "perseveration indicate organic distrubances, while order sequence" "curvature difficulty" "closure difficulty" and, also in this context "perceptual rotation" indicate emotional disturbances. These last items have been found to differentiate between well adjusted" children and children with different behavioral and emotional disturbances but without obvious signs of cerebral lesions (17).

Each deviation is given a scale value ranging from 1.0 to 10.0. The normal reproduction gives a scale value of 1 0.

The mean scale values for Bender items (Hutt) for the 3 groups of children are given in Table VI. Significant differences ($p<0.05$) between diabetic and control children are denoted by asterisks (31). The mean scale values of the in-

Table VI. Mean scale values for Bender items (Hutt) in CF diabetic and control children

Item	CF	Diab.	Control
Orderly sequence	6.90	2.42	6.56
Normal position (1st des.)	1.35	1.15*	2.18
Use of space	4.09	2.80	4.07
Collision	3.34	3.05	3.46
Shift of paper	1.46	2.39	2.63
Closure difficulty	4.79	5.38	2.41
Crossing difficulty	2.50	2.20	2.09
Curvature difficulty	4.37	4.35	2.64
Change in size and ang.	5.96	5.69	2.50
Perceptual rotation	7.84	3.08	2.05
Regression	1.93	2.02	2.16
Simplification	3.25	1.87	2.01
Fragmentation	2.03	1.11	1.81
Overlapping difficulty	2.82	1.61	1.36
Elaboration	1.09	1.11	1.55
Perseveration	4.65	2.68	1.59
Redrawing	2.55	1.99	2.10

dicators of organic disturbances for the 3 groups of children are given in Diagram XV.

A third type of *scoring, according to Koppitz* (66), gave no further information. It is however included in Table X and in the case studies as it gives an easily comprehensible summary of each individual child's performance. It also permits an evaluation of the drawings of children from 5 years of age.

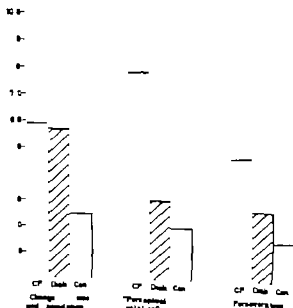


Diagram XV. Mean scale values of the indicators of organic disturbances (Hutt).

6. The Human Figure Drawing Test
n = 44 children above 5 years of age

The 30 "Emotional Indicators" isolated by Koppitz (67) according to their clinical ability to differentiate between children with and without emotional problems (see Methods) have been used in this investigation. The percentage of each of the 30 indicators found on HFD.s of 44 CF children above 5 years of age are shown in Table VII. They are compared with one group of 59 diabetic children above the age of 7 studied by Fällström (unpublished) and two groups from Koppitz validation material (67)—one group consisting of 76 children of average intelligence (WISC) from a child-guidance clinic and another group consisting of 76 children (paired with the clinic group), who were rated by their teachers as outstanding "all around" pupils, aged 5–12 years (well adjusted group).

Examples of deviations and interpretations of emotional indicators according to Koppitz is given in App. IV.

Two or more emotional indicators on a HFD are highly suggestive of emotional problems and unsatisfactory personal relationships (67). Table VIII gives the percentage of children in each of the 4 groups, who show the given number of emotional indicators on their *HFD.s.*

Considering all items, 58 % of both the CF group and the diabetic group, 72 % of the clinic group and 5 % of the well adjusted group showed 2 or more of those indicators which are highly suggestive of emotional problems. No child out of either the diabetic, clinic or the well adjusted group had more than 4 of these indicators on their *HFD:s. Five CF children, however, showed 5 or* more indicators.

In the case of the CF children, no relation to the child's medical condition or to the mother's "N" score on the EPI was found.

Table VII. Percentage of "Emotional Indicators" found on HFD:s in four different groups of children.

The 8 emotional indicators marked x) are found significantly more often on the HFD:s of children with brain injuries than on those of controls (67).

Significant differences between the CP group and the diabetic, clinic and well adjusted group resp. are denoted by asterisks. ($p < 0.05^{*}$ $p < 0.01^{**}$ $p < 0.001^{***}$) The Chi Square values are given in App. V

	Emotional Indicators	CP	Diab.	Clin.	Well adj.
		44	59	76	76
		%	%	%	%
Quality signs	x) Poor integration	11.4	13.6	11.8	0.0*
	Shading of face	11.4	1.7	3.9	0.0*
	Shading of body	9.1	0.0	13.1	1.3
	Shading of hands	4.5	0.0	6.6	0.0
	x) Asymmetry	15.9	27.0	6.6	0.0**
	x) Slanting figure	11.4	8.5	14.5	0.0*
	x) Tiny figure	2.3	28.8**	13.1	0.0
	Big figure	18.1	11.9	9.2	0.0***
	x) Transparencies	13.6	1.7	10.5	2.6
Special features	Tiny head	2.3	3.4	3.9	0.0
	Crossed eyes	0.0	0.0	0.0	0.0
	Teeth	11.4	0.0*	6.6	3.9
	Short arms	18.1	3.4*	14.5	3.9
	Long arms	11.4	0.0*	7.8	1.3
	Arms clinging to body	0.0	18.6**	5.2	2.6
	Big hands	4.5	1.7	6.6	0.0
	x) Hands cut off	13.6	5.1	14.5	3.9
	Legs together	4.5	16.9	3.9	2.6
	Genitals	4.5	0.0	2.6	0.0
	Monster	4.5	0.0	3.9	1.3
	Three figures	4.5	0.0	5.2	0.0
	Clouds	4.5	0.0	7.9	1.3
Omissions	No eyes	4.5	0.0	2.6	0.0
	No nose	13.6	3.4	7.9	2.6
	No mouth	4.5	1.7	5.2	0.0
	x) No body	2.3	3.4	5.2	0.0
	No arms	0.0	1.7	5.2	0.0
	No legs	6.8	6.8	0.0	0.0
	No feet	9.1	13.6	9.2	2.6
	x) No neck	2.3	6.8	9.2	0.0

Table VIII Number of emotional indicators in four groups of children s HFDs

Nr emotional indi-cators	CF	Diab.	Clinic	Well adj.
n =	44	59	76	76
	%	%	%	%
0	16	15	9	76
1	26	27	18	18
2	25	25	30	5
3	14	24	29	
4	9	9	13	
5	2			
6	7			
11	2			

CF/Diab	CF/Clinic	CF/Well adj
r=0 462	r=0.773	r=6.535
p<0 10	p<0.10	p<0.0001

Table IX. Nr of mothers showing each St. value on the EPI compared with the expected in a normative population.

Stanine	1	2	3	4	5	6	7	8	9	
Normal expected values	2	3 5	6	8,5	10	8 5	6	3 5	2	M 5 0
Extroversion n CF mothers	4	8	12	5	9	6	4	0	2	M 4,0
Neuroticism n CF mothers	1	2	6	6	7	8	8	8	4	M 5 7

7 The Eysenck Personality Inventory

According to Eysenck (27), little doubt exists that questionnaire responses, given under the usual conditions, give a reasonably valid picture of the subject s habitual behaviour pattern. The EPI sets out to measure 2 major dimensions of personality extroversion and neurotiusm. The inventory was given to the mothers to complete while the author tested the CF child.

The results show that the CF mothers, as a group, differ significantly from the expected on both dimensions extroversion and neuroticism (less extrovert, $p<0.001$ resp. more neurotic $p<0.01$). The mothers scores on the Lie scale were average with a mean score of 5.0.

Table X Summary of certain ratings and scores.

Child nr	Sex	Age	Medical cond.	Treatment time per day	Smallest or among smallest	Phys. str	Rate of absence	Craves att x "Uses CF=o"	Over protected	Mother's contact with and inf. to teacher	Curriculum difficulties	Embarrassed drugs	Embarrassed cough	Embarrassed go to toilet	Nocturnal enuresis	Sleeping difficulties	Bender score (Koppitz (66))	Nr emot ind H-F D (67)	Mother's EPI "E"	Mother's EPI "N"
								teachers ratings											stanine	
1	M	9·10	Mod.	31–60 min.	X		+						X	X		+	– 2 s. d.	4	1	8
2	F	8.2	Mod.	1–30 min.											+		– 1 s. d.	2	5	8
3	F	5.8	Very sev	2–4 hours													– 1 s. d	6	4	8
4	M	10.4	Mod.	no treatm.	X	–	+	X		more cont.	read writ.		X	X	+	+	– 3 s. d.	11	9	8
5	F	4.6	Exc.	1–2 hours											(+)	+			4	6
6	F	7.5	Mild	1–30 min.		–	+	X		more cont.	all subj	X		X			low aver.	2	7	7
7	F	7.0	Exc.	no treatm													low aver	6	7	7
8	F	10.4	Mild	1–30 mm			–			no inf							average	1	3	7
9	F	4.6	Very sev	2–4 hours											(+)				6	5
10	F	10.0	Mild	1–30 min.		+	–										high aver.	1	2	7
11	M	10.10	Mod	1–2 hours		+	+	X	X	more cont.					+		average	3	2	3
12	F	4.8	Mild	1–30 min.															6	7
13	F	7.0	Exc.	1–30 min.											(+)		– 1 s. d	2–3	5	5
14	F	11.5	Mod	1–2 hours		–											average	2	3	5
15	F	6.3	Mod.	1–2 hours											(+)		low aver	2	5	4
16	M	6.3	Mild	31–60 min.												+	high aver	0	6	4
17	F	11.1	Mild	no treatm.			+			no inf.			X				average	3	9	3
18	M	4.6	Mod	1–2 hours											(+)				5	6
19	F	5.0	Exc.	1–30 min.												+		2	5	3
20	M	6.1	Mod.	1–2 hours													high aver	1	3	8
21	F	5.0	Exc.	31–60 min.															2	9

23	F	15.1	Mild	1 30 min.	X					more cont.				X	+	+	−1 s.d	1	2	9
23	M	7 7	Severe	31–60 min.	X	−	+	O			sad. wrtt				+		−3 d	6	2	4
24	F	4.8	Severe	1–2 hours											(+)	+			2	2
25	M	14 7	Mod.	1–30 min.													average	1	6	3
26	M	15 1	Mod.	1 30 min.	X	−	+			no inf							−2 s.d.	2	3	5
27	F	12.0	Sever	1 2 hours	X		+	X	X	no inf	ll subj	X	X	X	+		low ver	1	1	8
28	F	8.8	Mod.	1 30 min.													−3 s.d	3	3	7
29	M	7 0	Exc.	1 2 hours											+		low aver	4	3	7
30	I	8.6	Severe	2–4 hours													low aver	1	3	7
31	F	4 9	Mod.	31–60 min															6	4
32	M	6.6	Mild	1 30 min.											(+)		−3 s.d	4	1	4
33	I	13.2	Exc.	31 60 min	X												−1 s.d	0	7	6
34	M	13 11	Mild	31–60 min.	X												−1 s.d	2	4	5
35	M	12 9	Severe	2–4 hours											+		verage	3	3	7
36	M	8 3	Mild	31–60 min	X		+			more cont.		X	X	X			1.5 s d	3	3	8
37	M	7.3	Mod.	2–4 hours	X					more cont.	read wrtt.						−1.5 s d	5	2	6
38	M	8.3	Mod	1 2 hours			+			less inf	all subj					+	2.5 s.d.	2	3	6
39	I	8 11	Severe	31 60 min	X							X	X	X			high aver	1	6	2
40	M	5 7	Mod	no treatm.											(+)		+1 s.d	1	1	9
41	F	15 1	Mild	1 30 min.	X												average	0	5	1
42	M	5.5	Mild	no treatm.												+	average	2	5	8
43	M	9.0	Mild	no treatm.	X			X				X	X				average	2	4	3
44	M	8 10	Severe	31 60 min.												+	low aver	0	3	5
45	M	12 11	Severe	1 2 hours													low aver	3	5	3
46	M	6.0	Mod	1 2 hours													low aver	0	2	5
47	F	6.3	Exc.	1 2 hours													low aver	1	3	7
48	M	5.4	Mild	no treatm.													high ver	4	7	6
49	M	9.6	Severe	2–4 hours	X	−		X			read. wrtt			X		+	average	2	4	9
50	F	11.5	Mod.	1 2 hours	X			O							+		1 s.d	0	5	6
51	M	4 7	Exc.	1 30 min.												+			3	6
52	M	6.7	Very sev	1–2 hours												+	low aver	1	7	4

V CASE STUDIES

I

Elizabeth, 6 years old, is a small but healthy looking little girl who has a medical condition of "excellent". She does not cough unless infected.

Eliszabeth's mother was 23 and her father 30 years old when she was born. Her mother started suspecting something was wrong with her daughter already 2 weeks after Elizabeth's birth on account of the child's 15–20 fatty and loose bowels a day.

Elizabeth was diagnosed as having CF 15 months later after having seen different doctors at least 15 times and after having been an in-patient in different hospitals for more than half a year.

The pre-diagnostic period was experienced by the mother as very difficult. Elizabeth cried for hours each night suffering from abdominal pains. Feeding was very frustrating as Elizabeth vomited as soon as she started eating and her stools were not only frequent and fatty but also very foul smelling. Elizabeth's mother states that she got no understanding from the physicians for Elizabeth's difficulties—they treated her as a fussy mother worried for nothing.

Elizabeth's mother experienced a sensation of relief when given the diagnosis of CF, an illness she had never heard of, thankful that a cause for all difficulties had at last been found. She was, during the 2 months Elizabeth was at the hospital, now and then told details about CF but nothing very distressing was said and she was not told that her daughter suffered from a severe, chronic illness. She was instructed in physical therapy and received drugs that almost completely removed the child's symptoms. A mist-tent was also supplied. It was not until the Swedish Association for Cystic Fibrosis was founded a year and a half later that a pertinent information about CF was given.

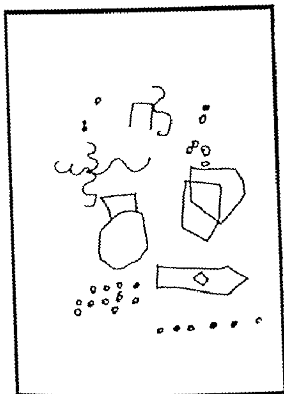
Elizabeth's parents are divorced, according to the mother on account of Elizabeth's illness. Her father refused to accept that there was something wrong with his daughter and her mother received no understanding, support or help from her husband who, the mother says, still does not know what CF is nor does he wish to know.

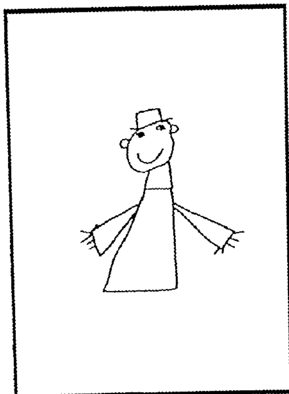
Elizabeth receives at least one and a half hours of inhalation and physical therapy a day divided into 2 "sessions", one in the morning and one in the evening. She hardly ever coughs up sputum during therapy unless infected. When she is ill therapy is given three-quarters of an hour every 2 hours. Breathing exercises are given once or twice a week. Elisabeth's mother finds therapy strenuous, especially weekends and holidays when the daily routine is different. Elisabeth, on the other hand, rather enjoys therapy and the close contact it offers with her mohter. She sings when her mother "thumps" her and says therapy makes her feel good.

The physician who treats Elizabeth orders much therapy to all his CF patients irrespective of their medical condition and this is one reason why Elizabeth gets a very large amount of treatment in relation to her excellent condition. Another reason, according to the mother, is that she, being single, feels she has to prove herself as capable as a "full" family to take care of her child.

Medication is no problem for Elizabeth. She swallows her 6 different kinds of pills without trouble. She no longer uses a mist-tent. She has the last year become aware of her illness and has started asking questions about it, but the questions are not yet difficult for her mother to answer.

Elizabeth and her mother have thus been living by themselves the past 3 years. The mother works part time as a teacher. She has the possibility to





Elizabeth (case no. 1).

stay at home when Elizabeth is ill as she has an understanding employer Thanks to the care allowance the mother receives for Elizabeth, the family does quite well economically in spite of the mother's short working hours.

Elizabeth goes to a kindergarten each day when her mother works. Her mother rates Elizabeth as being somewhat lonelier than other children. She likes to read or play quiet games with preferrably elder girls. Elizabeth s mother says she has not in any way spoilt her daughter and hopes she treats her no differently than she would had Elizabeth not been ill. However she feels somewhat isolated as she cannot afford the specially trained babysitters she feels she needs for her daughter She would like to have contact with other CF parents so that advice and support mutually could be given, but is, at the same time, afraid to indulge too much in CF

Bender

Elizabeth s Bender on account of her age only scored according to Koppitz (66), gives her a score of 11 The mean score for her age is 8.4 with a s.d. of 4 12. She falls within this range.

HFD

Only one emotional indicator omission of legs is found on Elizabeth s HFD This indicator is, according to Koppitz (67), extremely rare as legs are usually among the first parts of a human body that a pre-school child depicts. Legs tend to follow in developmental sequence right after the drawing of head and eyes, even before the child begins to draw bodies and arms. In Koppitz studies, this indicator reveals anxiety and insecurity

WISC

Elizabeth s IQ is low average.

EPI

Elizabeth s mother had an E" Stanine score of 3 and a N" score of 7

II.

Agneta, 10 years old, is a strong healthy and goodlooking girl who, on account of a not quite perfect chest X-ray has a medical condition of "mild" She is well within the normal height and weight percentil for her age and is, most of the time, able to compete in sports and games with her peers on their conditions. Her parents rate her as being no different from her friends and peers in any way having the same strength, endurance and apetite for life as they have. She is a happy natural girl who is popular with her friends to whom she has explained about her illness in a positive way Agneta does not cough when not infected.

When Agneta was 2–3 months old, her parents, then just under 30 years of age, started suspecting that something was wrong with their daughter She did not gain weight despite a voracious apetite and she, many times a day had very voluminous, foul-smelling stools. Agneta s pre-diagnostic period was very long—she was 4 years and 7 months when she at last was diagnosed. Her parents had by that time visited different private practising pediatricians and the pediatric clinic nearly once a month for 4 and a half years and Agneta had been an in patient in the hospital 5 times. Different drugs for different ailments had been tried, but none were successful. Agneta s mother was often depressed and felt very unsure of herself and isolated as she, on account of her daughters feeding problems, difficult and very foul-smelling stools and recurrent rectal prolapses felt she couldn t leave her daughter in anyone elses care, even for a few hours. During this period Agneta s healthy sister now 7 years old was born.

The parents did not react in any special way when the diagnosis finally was made, thinking this was just another false diagnosis. They were, according to the mother given no information about CF only the name, a prescription for pancreatic enzymes and antibiotics, a short instruction in physical therapy and a reservation for the next visit to the clinic, 3 months later The parents made no real attempt to find out what CF was and did not learn, more than sporadic details, until the Swedish Association for Cystic Fibrosis was founded and Agneta was nearly 7 years old.

Agneta receives 15—20 minutes of physical therapy each day twice a day when infected. The therapy is both given and received without too much trouble. Dark winter mornings when it is difficult to get out of bed and weekends and holidays when there is no routine to fall back upon are sometimes a bit stressful. Agneta s father as a rule gives her therapy once or twice a week during the week-end and also helps with administering drugs, while the mother who is quite content not to work outside the home, treats Agneta the rest of the week.

The parents mutual relationship has always been good and has, according to the mother grown even better with the problems the parents have gone through together They are able to speak freely with each other about all aspects of CF and they feel they give each other very valuable support.

Agneta started questioning her parents about her illness before the parents themselves knew more than details about CF After they had become enlightened, they have always tried to be "ahead" of their daughter in their explanations, discussing different aspects of the illness with her before the questions come about, something which has been very satisfactory in this family

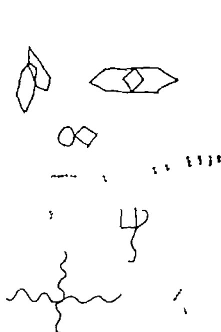
The mother states that she has no problems with Agneta s healthy sister and that she has plenty of time left for her second daughter s needs. The parents do not give in easily to Agneta, she gets no special favours and she is treated just like her sister The parents do not feel isolated on account of CF

Bender

Agneta is scored for i.a. assymetry and she often exchanges circles for dots. Her Bender score, however is according to all 3 scoring systems normal for her age.

HFD

"Clouds" is the only emotional indicator on Agneta s HFD Koppitz hypothezized that the spontaneous addition of clouds indicates that the child feels threatened by the adult world.





Agneta (case II).

WISC.

Agneta's IQ is bright normal.

EPI

Agneta's mother has an "E" Stanine score of 5 and a "N" score of 1

Teacher

Agneta is perfectly average in the school situation. Her rate of absence is lower than normal for the class as a whole. Her mother has not informed the teacher about CF

III.

Peter is 8 years old, the third of 6 children, 2 of who have CF born to parents where the father at the date of test and interview was 37 and the mother 36 years old.

The family is one of the few in Sweden with suspected CF in earlier generations. The mother had 5 siblings who died before 2 years of age in a mysterious abdominal illness No suspected cases of CF is known in the father's family

Until half a year ago Peter's family lived on an island off the east coast of Sweden where the family for generations had made its living keeping a small farm. The impossibility of proper medical care for 2 CF children has forced the family to move to a town with better medical facilities. The family now lives in a typical newbuilt suburban 4-room apartment where most of them are unhappy especially the father for whom moving to a town has resulted in a depression. The mother explained that the father had hardly "spoken a word" since they had moved into the apartment. The family was now on welfare as the father had no experience in any city job. Being a "social case" made the situation all the more difficult for the father as he and his family had always been able to support their wives and children. He was to start a re-education course within soon but could not summon up any interest for this.

Peter's parents had been married 3 years when Peter was born. After 3 months his parents

started, on account of serious feeding and toilet problems to suspect that something was wrong with their son. After several visits to a Child Care Center he was referred to the pediatric clinic in the provincial town nearest to where the family lived, and the diagnosis of CF was made one month later *This month was full of considerable stress* for the mother as she was too inhibited, respectful and anxious to dare ask what was being done with her child. The diagnosis was given on the telephone and the mother was told her son had something wrong with his stomach which, however could be treated with drugs. In spite of the reassuring diagnosis (only something with the stomach), the parents were very worried thinking of the mother's 5 siblings who had all died at a very young age in what was apparently the same illness. They were given no information about CF and only learned what the illness was when the Swedish Association for Cystic Fibrosis was founded 5 years later Up till then no therapy was given except for pancreatic enzymes.

The parents were given genetic counselling after Peter's diagnosis and they had understood the meaning of what was told. The counselling physician *was negative to the couple having further* children. However with the explanation that they both of them love children and that it "just happened 3 more children were born within 3 years, the youngest, a boy of 5 also with CF The mother exhibits no regret but says they will now have no more children.

Peter's medical condition is "moderate He is a frail-looking, rather shy boy His younger CF brother appears to be in better health both physically and socially

Peter is given one hour of physical therapy twice a day when not infected, 3 times a day when ill. He coughs up a moderate amount of sputum during each session and, as a rule, also coughs in the time between. His mother finds the therapy strenuous (Peter's CF brother also receives an hour of therapy each day) even if it is part of the everyday routine. The father only helps if it is absolutely necessary (mother away or ill). Peter dislikes getting therapy but as a rule co-operates even if he often is irritated and says he would rather die than be forced always to have it. When he does not co-operate, his mother threatens him with the hospital.

Peter has monthly routine controls at the pediatric clinic where different doctors see him at nearly every visit. In addition to this, Peter and his *CF brother are in-patients at the hospital every* third month for one week for a thorough check up.

Peter eats 8 different kinds of drugs, of some of them many pills a day He eats them without difficulty and medication is no problem for him. Peter's diet, high in proteins, low in fats, is not a problem either on the contrary it is good for the entire family

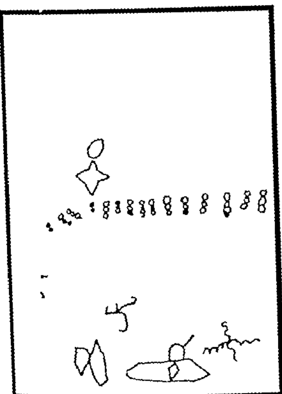
Peter started asking questions about his illness at 6–7 years of age. The parents feel prepared when questions come and try to answer truthfully but without frightening their son. He seldom talks about this illness.

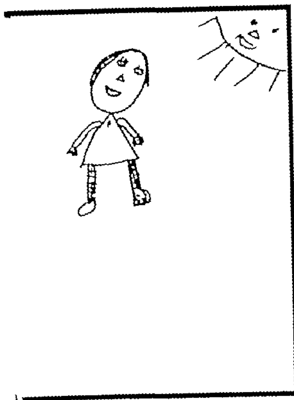
The mother thinks Peter is a little lonelier than other children. *The last half year* in the town where they are now living has been especially difficult for him as he up till now has been used to few peers and a very small school. *Although Peter's mother has explained about CF* to new friends and neighbours, these are still afraid of the boy's cough and often try to avoid him. Peter tries to compensate for his illness through playing monkey

According to the mother the parents could earlier communicate freely with each other about CF Since they moved into the town, however her husband has, as related earlier hardly said a word

The mother has a bad conscience as the care of the CF boys takes so much time that she does not have enough energy left for the other 4 children, especially not when the CF boys are ill. The other children are often jealous of their brothers, especially the eldest girl (15 years of age).

Peter's mother feels that she in many ways spoils her CF sons and lets them have their own way although she knows this is not good for them. She does not want to deny them anything as they have to go through so much each day that is spared other children.





Peter (case III).

CF isolates Peter's parents. They feel they are stationary where they are with no possibility to go away for a week-end, holiday etc. as equipment in cluding 2 mist-tents always has to be brought along. Meeting other people is also difficult as there is always bound to be a cold somewhere.

Bender
Peter's Bender reveals a very severe perceptual-motor disturbance. He is i.a. scored for "work over" rotation distortion assymetry and perseveration. Most of these deviations are, ac cording to all 3 scoring systems, significantly more often found in children with neurological dis turbances. Peter's score, according to Koppitz, is nearly 3 s.d. below normative for his age.

HFD
Two emotional indicators, shading of hands and slanting figure appear on Peter's HFD. Shading of hands is often found among shy and aggressive children, while a slanting figure was, by Koppitz, observed on HFD.s of children ranging all the way from mildly upset to severely disturbed. Peter has also added a crying sun to his HFD—perhaps a projection of an emotion to somewhere where it is safer to express it.

WISC
Peter's IQ is low average.

EPI
Peter's mother has an "E" Stanine score of 3 and a "N" score of 6.

Teacher
Peter is physically somewhat weaker than his peers. His rate of absence is much higher than average for the class. Peter's mother has informed the teacher about CF but she has less contact with the teacher than what is normal for the mothers in the class. Peter has difficulties with all subjects in school, but he is improving immensely. He has, however marked difficulties in reading and writing.

IV

Carl is a 6 year old frail looking little boy with a more or less continous cough. His medical condition is "severe" Each of the 3 times the author saw him he was dressed in his home town football team outfit.

Carl's parents were both 25 years old when Carl, their first child, was born. Four months after his birth it was clear to them that something was wrong with their son. He vomited several times each time he ate, had fatty foul smelling stools and a whooping-like sounding cough. His parents were worried but at the same time his mother was happy to have a child who needed her so much. *She believed his troubles came from her breast* feeding him. Four months later after having been seen by several different physicians, Carl was made an in-patient at the pediatric clinic in the city where the family lived. The parents, escpecially the mother became very upset and worried and the mother states she hardly slept during the month Carl was at the hospital.

When the diagnosis was made the parents were given very little information about CF and no information about treatment. They were told that his pancreas was in a bad shape and that they *should not hope too much. The doctor was very* understanding and sympathetic and did his best to help the mother who completely broke down during the days after the diagnosis had been given. She repeatedly left home in the night when her husband was asleep and went to the hospital where she walked back and forth weeping under Carl's window until her husband found her and brought her back home. Carl's father according to the mother was more calm and stable and gave the mother much support. The mother on the other hand, states she was then definitely in need of psychiatric help, but she did not have the energy to ask for it.

The parents received genetic counselling from a doctor who was very negative in his attitude to further children. When, however 2 years later another baby was expected, the doctor gave support and encouragement to the couple. A healthy sister was born.

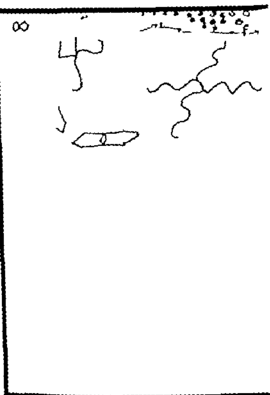
Carl's condition has, according to his mother grown worse during the last year He does not have the strength to play with other boys of his age in their more or less rough games but he does not want to admit this to himself He tries desperately not to show that he is sick, tries unsuccessfully not to cough when people outside his immediate family are present and is, according to his mother an unhappy angry and very negative little boy He often cries when he sees that other children can do things outside his limits. He does not want to discuss his illness with anyone. He mostly plays with girls who are kind to him. It is very important to him that they are of his age or older

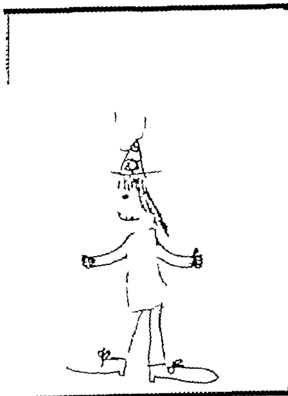
Carl receives nearly 4 hours of physical therapy a day when not infected, and at least 10 hours a day when ill. Once a week he is taken to a physical therapist at the hospital, where he gets physical- and inhalation therapy the latter not given at home. These weekly sessions are a great help for the mother who experiences a feeling of security from the therapist with whom she can discuss all her problems. As a rule Carl's father except on the "therapist day" gives his son all his treatment and takes care of and cleans Carl's mist-tent. Carl himself hates having therapy but knows it is vital *for him. Holidays and weekends when there is no* special hurry are the least stressful.

Medication is no problem for Carl but his mother is very worried about the side effects of his drugs, being afraid they will hurt Carl so much that when a "cure *for* CF at last is *found* be will be too sick from the side effects of the drugs to benefit"

Carl became aware of his illness around the age of 4 when he observed that his younger sister neither got therapy nor pills. His questions were relatively easy to answer until he started school. During the last year the questions have become more difficult to answer and especially the mother has great difficulty in coping with her own feelings when questions are asked. Carl often asks about death but never in relation to himself Most pictures he looks at, according to the mother to him resembles lungs.

The parents have always been very close to one another but the mother incessantly feels guilty as





Carl (case IV).

she gives Carl 75 % of her time while her daughter and husband have to share the rest. The mother does not believe this has hurt her daughter although she states that her husband believes it has. He notices that the little girl always, in different ways, tries to get attention, and the father has lately tried to be with her as much as time will permit.

Carl's mother says she spoils her son, wanting to compensate for everything he misses and everything he has to go through. She says she treats her 2 children very differently. She does not perceive her care as overprotective, although she dresses and undresses her son, often feeds him and several times a week carries him to school. He is able to do these things by himself.

Carl's parents feel isolated. They are afraid of catching infections and they have trouble finding babysitters they can trust. They do not enjoy meeting other families as they feel they cannot plan ahead as other parents do. On the other hand, meeting regularly with other parents of CF children would be unbearable as only CF problems would then be discussed.

Before Carl was born, his mother worked as a secretary. She sometimes feels bitter that Carl's illness must keep her at home, but at the same time says she could never trust his care to anyone else.

Bender

Carl's Bender is scored for i.a. rotation and assymetry these 2 indicators being found significantly more often, according all 3 scoring systems, on the Bender records of children with neurological impairment. He reveals closure difficulties and his figures are constricted. His Bender suggests a mild to moderate degree of perceptual disturbance for his age.

HFD

Two emotional indicators, partial shading of the face and a grotesque figure" A grotesque figure does not seem to be associated with any specific type of behaviour but rather reflects feelings of in-

tense inadequacy and a very poor self-concept. Children who draw grotesque figures seem to perceive themselves as being different from others or think of themselves as rather ridiculous individuals who are laughed at and not fully accepted by others.

WISC
Carl's IQ is bright normal.

EPI
Carl's mother has an "E" Stanine score of 4 and a "N" score of 9

Teacher
Carl is among the smallest in his class and is physically very much weaker than his peers. He is, however not aware of this. His rate of absence is no greater than what is normal and his social position among peers is also normal. Carl craves a lot of attention and sometimes talks to his teacher about his illness. Carl is not embarrassed for his cough in school. He has difficulties in reading and writing but receives no extra help. He does not eat lunch in school. He participates in gym.

V
Monica, 5 years old, is the fourth of 4 children, the 2 youngest with CF The father is at the date of test and interview 41 and the mother 27 years of age.

When Monica was born, her then still undiagnosed CF sister was 2 years old. Treating, worrying for and concentrating on the latter little girl's repeated infections and pneumonias prevented the mother from taking too much notice of Monica's symptoms until she was 8 months old. At this age Monica had serious feeding problems and could have 20 to 25 fatty and loose stools a day She was taken to the pediatric hospital where her sister at that time was an inpatient and the 2 girls were diagnosed at the same time as having CF

The mother was immediately given a considerable amount of information about CF but could assimilate little more than that the disease was fatal. She, in her own words, heard the physician's voice a long, long way off but felt nothing" The father was not present when the diagnosis was given The mother was given a booklet about CF to take home and the delayed shock came some days later when reading this information.

Monica's mother spoke with no outsider about CF for a whole year She isolated herself completely couldn't bear to see healthy children, didn't want to go out of the house or have anyone visit her The parents relationship grew strained with the burden of the sick girls and they could only speak to each other about very trivial problems and very trivial aspects of their daughters illness, both of them "locked up" with their own anxiety The father insisted that the illness came from the mother's family (the mother's father had died in pulmonary tuberculosis) and would not accept that he too, was a carrier My husband" says the mother "had problems of his own in addition to our daughters, but I was too full of my own to try to find out what they were or to care and bother over how he felt" The mother started taking tranquilizers with which she has continued.

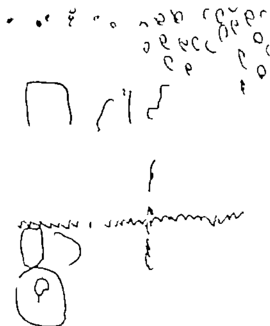
Monica's sister died when Monica was 2 years old.

Monica is an extremely frail, pale and small little girl with cyanotic lips and clubbed fingers. Her medical condition is "very severe" She has, for the past few years, required oxygen intermittently at present every night, and she has been extremely ill only half a year ago when she spent several months at the hospital. Monica gets 3 to 4 hours of therapy each day when not infected and 10 to 12 hours a day when ill. She coughs up sputum every few minutes. She has, when not infected, 8 different kinds of drugs. Monica's mother experiences the therapy as very strenuous. With therapy inhalations, getting the mist tent ready for the night and cleaning it in the morning, administering drugs and cooking special diet, CF obviously occupies most of the mother's day Being able to help Monica, however makes the burden somewhat easier to bear Weekends and holidays are worst as there on these occasions is no routine. Monica's father has an occupation which permits



Monica (case V).





Monica (case V).

him to choose his own working hours. He is often at home in the afternoon and then does Monica's afternoon therapy

Monica accepts her therapy as it makes her feel better but she often cries and is desperately tired of it. She suffers very much from her illness.

Monica started to be aware of the fact that she was sick already at 3 years of age and at this time also started asking questions, mostly the question "why?" Why am I sick" "why do I cough" "why am I so tired" "why do I always have to have therapy?" Her mother tries to answer truthfully but often finds it difficult to cope with her own feelings when her daughter is unhappy

Monica's mother has a very realistic view of her daughter's situation and states that she does not dare think and plan more than a day ahead. She is very much aware of the fact that Monica is a very lonely little girl. Monica does not have the strength to play with other children in their more or less wild games. She is very sensitive and she does not feel at ease with other children. At one occasion when Monica was on the playground with her mother a girl who was somewhat older than Monica had summoned all other children, pointed at Monica and said. "that little girl is very sick, she is not like us and we have to be especially nice to her" This hurt Monica deeply and she often refers to it. She does her best not to cough in the presence of peers and always hides her finger tips in the palms of her hands. Other children have at several occasions made fun of her clubbed fingers. Several times when Monica was younger and came to play in the sandbox, other mothers would remove their children saying here comes that disgusting coughing girl again Audible remarks have been made at the mother's selfishness in bringing a child with such a bad cough into public places. All these incidents have left deep scars in both Monica and her mother

Monica does not like staying at the hospital and has recently become frighetened as she during the last period had to go through so much. Hospital periods are also very strenuous for the mother

who is permitted to be there the whole time with her daughter partly because Monica insists on it and partly because her help is needed in caring for Monica.

The 2 other children in the family a boy of 13 and a girl of 15 have, since they were 5 and 8 years of age, and their first sick sister was born, very much had to take care of themselves and solve their own problems. They love their little sister deeply and try in many ways to give their mother moral support.

Monica s parents are aware of the fact that they often give in to her They try however to spoil her only in more or less unimportant things.

The parents, especially the mother feel ex tremely isolated. The family lives in a suburb and the parents have not had the energy to make friends with anyone. Neighbours don't understand their problems and the mother is too tired to go into details with people she doesn't really care about.

Bender

Monica s score on the Bender test, scored only ac cording to Koppitz on account of her age, is more than one s.d. below normative for her age group. She i.a. rotates several figures and perseverates in one figure into continuing drawing the figure on the back of her HFD sheet. Her Bender reveals a mild perceptual motor disturbance.

HFD

Monica s HFD shows the self image of a very sick little girl with her stomach full of mucus. When Monica was asked what the little girl's she had drawn good sides were, she answered "the left side" indicating the side where her lungs were least affected. Monica s HFD shows, in relation to her age, 6 valid emotional indicators, "assymetry slanting figure" "transparency" short arms genitals" and "no nose" revealing a ery severe disturbance. Transparencies of specific body areas are very unusual at any age and usually point to acute anxiety conflict or fear The presence of genitals or of symbols of them is a sign of acute body anxiety (Monica had started to get pubic hair secondary to being on anabolic steroids. This might account for her drawing genitals.)

WISC

Monica s IQ is average for her age.

EPI

Monica s mother has an "E" Stanine score of 5 and a "N" score of 8.

VI.

Stephan was 15 years old when seen by the author His medical condition was moderate. Stephan is the family's second child. Eight years prior to his birth a brother was born who died only 2 days old. The parents were told his stomach was destroyed" Stephan was diagnosed as having Pancreas Fibrosis when he was only 5 months old. The parents were told that their son had a lethal illness and that nothing could be done. He was prescribed enzymes, but no treatment or other drugs were ordained. The parents were told to try to lead as ordinary a life as possible and nothing was said of coming back for controls.

Sephan managed quite well the following years, and it was not until he was 7 years of age that his illness was properly brought to the attention of an interested pediatrician. Information about CF was given and a treatment plan was started. As Stephan was of school age when the first proper information about CF was given, he participated in all discussions concerning his illness of which still very little was known in Sweden. Thus Stephan has always known as much about CF as has his parents.

When, at 15 years of age, Stephan was tested with the WISC by the author he obtained very superior scores with placement in Stanine 9 on all subtests but one. His maturity level was far beyond average for his age.

Stephan was unable to participate in many of the activities of his peers as he was not strong enough. He was ashamed of his thin body He did not want to swim in the summer as this would in volve showing his body and he tried to find ex cuses for not participating in gym in school. He was ashamed of his cough. He tried to compensate

for these defects through hobbies and interests, some of which he shared with friends. He thus had an enormous aquarium, enjoyed fishing and loved to read. His favorite subject was mathematics, and problemsolving was as a hobby for him. After having finished school he proposed to go to the university or to an economical college in order to become an economist.

The answers obtained from Stephan's teacher on the questionnaire did not give much information about the boy's situation in school. The teacher stated that Stephan was the smallest in his class and that his position among peers was average. His rate of absence was relatively high, but in spite of this Stephan did very well in all subjects but gym and music.

Stephan was, according to the author an *adolescent who had adjusted fairly well to his illness.* He tried to make the best of his situation, had a good sense of humor and was relatively confident in respect to his future.

During the last 2 years the author has met Stephan's father at the annual meetings arranged by the Swedish Association for Cystic Fibrosis. His father is distressed as Stephan has lost all his self-confidence. His motivation to make the best of his situation and his ambition to study and go to the university as were his earlier intentions, have vanished. Stephan has become aware of the severe restrictions which will be put upon him through his illness when applying for an employment in the future.

In Sweden, a health certificate is nearly always required from an applicant to a job. Furthermore, the law is such, that an employer is not allowed to dismiss a person once appointed (104). This fact tends to make an employer hesitant to hire an applicant not in excellent health.

Thus Stephan has become despondent of getting a proper job after his studies. Pursuing a *profession through hard work seems utterly* meaningless and the prospect of an adult life, possibly with work attained through enforcement laws or someones good will, or if not, with a pension, has deprived Stephan of all hope for the future.

IV GENERAL DISCUSSION

Material

Four and a half years of age was chosen as a lower age limit for children to be included in the study while it was thought that by this age testing would be more valid and meaningful.

A true random sample of first 30 school- and then 22 pre-school CF children in Sweden was obtained and no respect was paid to the child's medical condition, to where the family lived or to by whom the child was treated. An overrepresentation of school children was deliberately picked as it was thought that a better picture of the child's development in respect to emotional condition, peers etc. could be reached at a somewhat higher age. In addition to this it was thought that certain problems would not evolve before the child reached school age.

A slight overrepresentation of severely ill children was randomly obtained.

In all but 3 cases, the child and its mother were both willing and anxious to take part in the investigation. In 3 cases the parents initially disliked the thought of participating but later agreed when the importance of a random sample was explained to them. No missing cases were thus obtained.

Methods

Psychological tests were chosen that

a. emphasize the presence of visual motor and emotional disturbances and
b. offered interesting comparison material with regard to an earlier study (31) on diabetic children.

The Rorsach test was included for the first 25 children tested. The results will be presented at a later date.

The E.P.I. was included to give a reasonably valid picture of the mothers habitual behaviour pattern and degree of neuroticism.

The interview was carefully structured to cover what was considered the most prominent problems for a family with a CF child. Care had to be taken not to ask questions that would be considered too personal or intimate. The problems of the healthy siblings of the CF child have been only briefly dealt with. This group of children needs more attention and should be investigated more closely

It would have been desirable to give the same interview to both parents separately but in the case of the very time-consuming interview required this was not possible. The mothers were chosen as they were considered to be the main care-takers of the children, most of the time administering therapy etc. Also, in the cases of chronic diseases, the mother is thought to have specific influence on the child's reaction to his disease (5 90). It would also be highly desirable to give the same interview to mothers of children with other handicaps.

There was initially no intention to give the teachers a questionnaire, but, after having interviewed a number of mothers it was thought desirable to include the teachers view of the child. The questionnaire was sent to the teachers of 24 school children. Twentytwo answers were obtained. The teachers of 6 school children who had died in the time between testing and questionnaire did not receive a questionnaire. It was thought that these teachers would have difficulty in giving objective answers to the questions posed.

The pre-diagnostic and diagnostic phases

The pre-diagnostic and diagnostic periods seem to be of great importance for the future adaptation of

the parents to their child's illness (69 89), and of secondary importance for the adaptation of the child. It is probable that the more time and energy the doctor can give the parents during these very vital periods, the better armed the parents will be to meet the future, both in terms of coping with the disease and in terms of contact with, and trust in, physicians.

Telling parents that their child has a serious illness is a difficult task for any doctor Franklin (29) has compared it to "the performance of a surgical operation without an anesthethic" When giving the diagnosis, the physician has two main functions to relate factual information and to help the parents with their emotional feelings. It is not surprising that many doctors, from the parents point of view fail in this task (53 74 81). This was frequently the case when the reaction of shock was experienced. When in a state of shock, people tend to react to the flow of information in a certain way The acute state of crisis characteristically inhibits the capacity to grasp what is being said (22, 42, 45b) and thus is often true even if the patient, or in this case the parents, ask intelligent questions and give the doctor reason to assume that what has been said has been understood. Sufficient time and privacy must be made available at successive visits to the clinic, the first preferrably only a few days after the diagnosis has been given, to allow the patient/parents to ask their questions, repetitiously if needed, as this is one of the processes which will enable them to accept the serious diagnosis. It is a mistake therefore, as was very often the case with the parents in this investigation, to arrange this important interview just before the discharge of the child from the hospital when it may be difficult to schedule conveniently the important follow up consultations. The physician must, with tact and sensitivity for the parents reactions, explain the nature of the illness, its etiology its treatment and its prognosis in a delicate balance between honesty and cautious optimism and in words that the parents can understand. Sincerity and empathy are here called for

It is of great importance that physicians and other medical personnel are aware of the patient's/parent's possible reactions to a serious diagnosis. This insight can be had through informal discussions about the patients and perhaps also through formal lectures or seminars with discussions.

In 32 % of the cases in this study the mother was given the diagnosis without the father being present. It is, however extremely important that both parents are given the diagnosis together preferrably by a doctor familiar with them, as being told by a stranger makes it difficult to express the intense emotions often experienced (32). Extremely helpful for most parents would be if a visiting nurse, lay person or experienced medical social worker who is well familiar with CF could come to the home of the newly diagnosed child to sit down and discuss all new problems. The need they had felt at that time for such help was expressed by nearly all mothers.

It is certainly not possible to determine how much of the parents view of the manner/amount of information given them during the period of diagnosis that is a function of the parents own perceptions and how much that is a function of the actual actions of the physician. Nevertheless, from the descriptions given of the pre-diagnostic and diagnostic phases, it would appear as if the majority of parents would appreciate a straightforward and honest approach from a sympathetic doctor who does not deprive them of all hope.

Regrettably long pre-diagnostic phases as the ones revealed in this study are not a thing of the past. The longest pre-diagnostic period of a child being diagnosed as having CF 1976 was more than 12 years.

A large group of parents who received inadequate information at the time of diagnosis did not on their own accord later seek more information. This was the case in 38 % of the entire group. This contrasts to the findings in other countries concerning the behaviour of parents of children with other serious chronical illnesses. For example, parents of children with Tay Sach's disease (53) in various ways tried to seek information as did parents of children with malignant diseases (42). Mattsson and Agle (83) found that many parents of boys with hemophilia made it a point to learn all

they could about the medical and even the psychological aspects of the disease thus helping them master their anxiety and helplessness via a control through thinking. Obviously even parents of CF children use this mechanism, but the percentage who remain ignorant for a long time is substantial. This finding is remarkable as these parents in many cases were the very ones who had shown great initiative in their struggle to attain a correct diagnosis.

The Long Term Adaptive Phase

Genetic information and counselling

Genetic counselling is an integral part of any medical problem wherein hereditary factors are either suspected or proven. As reported earlier (26, 44, 95) the effect of genetic counselling as a prohibitive factor against producing further children in families with a recessive inherited disease is limited. Meyerowitz and Kaplan (89) reported that CF parents who had previously suffered the loss of a child were significantly more likely to bear further children than parents who had not suffered a loss. It was assumed that further child-bearing was a denial of guilt reaction. The authors, however, do not indicate whether these parents were fully aware of the genetic risks involved in bearing further children. Tips et al. (112), on the other hand, report that fear and anxiety in families with hereditary diseases may spread throughout the entire kindred to include individuals who are not at genetic risk resulting in significant reduction in reproduction.

The interpersonal attitude to risks differ widely and the personal, subjective interpretation of odds has a major influence on the decision parents ultimately make in what can be regarded as a clinical gambling situation (95). The manner in which risk figures are expressed may have a significant influence on how the individual interprets them. The same objective risk for known heterozygotes for a recessive gene may be expressed as either a 1 out of 4 risk of the disease occurring, or alternatively as a 3 to 1 chance that the child will be normal. If a serious, chronic genetic disease occurs in a first child, the interpretation of recurrent risk to subsequent children will, according to Pearn (95) be modified. On the other hand, the natural desire for children, or for at least one healthy child, is very great, and will tend to conflict with the disproportionate weighing effect of the first child being affected. In the present material these findings were verified. Parents whose first child was affected, were (after correct genetic information) more likely to have a further child than were parents who already had a healthy child in addition to a CF child. The finding was, however, not statistically significant. According to Hecht (44) and Pearn (95), another factor that highly affects the parents attitude towards having further children is the degree of burden imposed by the disease. This factor is, according to these authors, sometimes greater than the magnitude of the recurrance risk of the disease but it was not expressed by any of the parents in this study.

It is of great importance that the physician who gives genetic information knows a great deal about the illness concerned and that he has the capacity to explain to the parents in terms that they can understand. It is useless if genetically counselled parents think—as in 4 families in this study—that they will conceive 3 healthy children before a second CF child is born. The probability that the physician can give genetic information in a manner which the family can understand and utilize is greater the more he knows about their intellectual, social and psychological background and of their present emotional state. The genetic mechanisms must at times, as is shown in this investigation, be explained only in the very simplest of terms. Principles should be emphasized rather than mathematical terms. A good complement would be written information that the parents can study on their own.

Emery et al. (26) has reported the existence of an emotional barrier to the comprehension of genetic information during the initial period of overwhelming anxiety created by the diagnosis. He therefore recommended that genetic counselling not be given too soon after the diagnosis is reached, and that it be repeated with both parents present.

Obviously the physician who gives the genetic information can not decide whether the parents should have further children or not. The physician has no possibility of knowing how strongly the family desires another child, how prepared they are to care for another possibly ill, child, what religous and ethical values the parents have, how great the pressure on the parents is from relatives and friends a.s.o. The parents should be fully informed about all genetic aspects of the illness, but the decision must always be left to them and whatever decision the parents make should be supported by the physician. If another CF child is born to parents who have been definitely advised against another child, even greater guilt feelings would probably ensue than had the doctor been neutral. A great value of genetic counselling and information also lies in the fact that the parents know what they are "up against" and do not feel "cheated" into another CF child.

The importance of an early diagnosis (preferrably newborn screening) to enable the parents to receive genetic information before another child is conceived, must be stressed as must the urgency of a reliable method for prenatal diagnosis.

Current contact with physicians

Three factors, made clear during the course of this study which are important for the care of the CF family are

1. Continuity in the care of the patient (one doctor).
2. Possibility of specialist consultation (regional centers).
3. Same treatment methods in the whole country

A chronical and serious condition results in long-term needs for both the parents and the child. These needs cannot be met by irregular and sporadic treatment by a variety of everchanging medical personnel (74). The long-term availability of one physician to the family his continious, personalized support of their positive actions and understanding for their feelings, his willingness to provide and *volunteer* information and to correct misunderstandings are vital to the child's progress and to the parents adaptation. A physician who knows the family well can see psychological problems "coming up" in parents as well as child, and maybe prevent them. As in all areas of medicine, prevention is far more effective than treatment of pathological changes (2).

Taylor et al. (110) suggest a model where a well trained social worker acts as an extension of the physician. She should be trained to identify gaps in the parents understanding of the disease and be able to provide the physician with supplementary information regarding the feelings of the family the parents attitudes and their receptiveness to additional information. She should be able to logically supplement this information from time to time and provide the impetus for the physician to efficiently intervene, amplify and explain under optimal circumstances. At the same time she could provide the parents with the opportunity to talk to someone who understands their problems and who has time to listen to them. She could help arrange practical details and give emotional support when difficulties arise. The need for such a person to the majority of families in this study was obvious.

This and earlier (11) investigations clearly show that the personality of the doctor is very important. Thus parents were satisfied with their doctor even if he did not appear to know very much about CF if only he was interested, did what the parents felt was his "very best" and gave them support. Competent care, however is vital and regional centers with a skilled CF team led by an interested and capable physician is desirable.

Some parents experienced a definite conflict between their own physician s treatment methods and the method recommended by the "RfCF doctors" They were worried as to whether they gave their children optimal care or not. Much effort however has lately been made to get a unified design of the treatment in general for the whole country In details, of course, the treatment must be arbitral (see App. VI).

The parents mutual relationship and communication

Many mothers, belonging to the group of 36 couples whose relationship was unchanged or better claimed that they and their husband found their common problem with CF so important that they never quarreled or argued about anything any more. It might be that the CF child in these families was used as a conflict avoiding tool" (73). Thus confrontations involving difference in opinion, marital problems etc. were often avoided and detours constantly made to bypass any kind of conflict, resulting in ineffective or defective communication within the family Three teenage boys who had never brought up the subject of their illness with their parents nor the parents with them, all had parents belonging to this group.

The parents of severely ill children seemed to be able to communicate better on the subject of their child's health than did the parents of children with excellent, mild or moderate symptoms. The reason for this might be the severely ill child's obtrusive signs of illness, obvious both to the parents and the ill child.

Among the 13 couples whose relationship had grown worse, only 3 were able to communicate freely on the subject of CF Another kind of problem seemed to be present in several of these families. The mother often seemed to be overinvolved with the CF child regardless of his medical condition, and neglected or did not have energy or time left for the needs of the rest of the family The father in many cases, seemed to be a peripheral figure who was expelled from the mother-child unit. The parents were unable not only to communicate on CF but also to communicate on most other subjects. These findings are in accord with those of several other investigators. Thus Kulczycki et al. (69) and Turk (114) found, often severe, problems of communication in CF families and Kanof et al. (53) found alterations in the patterns of communication in families of a child with Tay Sach s disease—although 50 % of the couples in this study at the same time reported an improved relationship as a result of the illness in their child. Linder (76), who did group work with parents of handicapped children in general found that virtually all mothers reported that the topic of the child's disability was not talked of at home. The role of the father as being expelled to an out sider has also been found among CF families by Boyle et al. (12), among fathers of children with asthma (73), hemophilia (2), Tay Sach s disease (53) and handicaps in general (38).

A child with CF—or with another chronic disease—thus seems to be a powerful source of either unity or disunity although it may be hypothezied that the illness usually accentuates pre-existing marriage problems rather than causes them.

When one member of a family suffers, most often all suffer and the concern must be, not only the "total child look" but also the "total family look" For this reason both parents should, as often as possible, be present at the child's visit to the clinic. Many mothers reported difficulties interpreting and aswering their husbands questions about problems they did not clearly understand themselves. Establishing adequate communication is vital for the familys coping process but difficult in any marriage. To find the words to support one another in this problem often seems impossible. An objective person through whom to talk, is very often needed.

Group therapy for parents of chronically ill children has been recommended by Mattsson and Agle (83) who found a continued improvement in the selfconfidence of the group as parents of chronically ill children. Therapy was particularly helpful for those parents whose ability to learn and use instructions was crippled by a lack of awareness of their affective responses and methods of adaptation. Group therapy has also been found effective among parents of mentally retarded children (101), hemophilic children (83) and children with cerebral palsy (45a). McCollum and Gibson (86) have suggested that group discussions for parents of CF children are useful, making available to each parent a cor porate body of experience. The parents in Boyle s et al. study (12) expressed a need for such a group endeavour However even if group therapy may give support to certain individual CF families, great precaution is certainly necessary when inviting parents to participate. In her resumé of

parent groups in pediatric practice, Korsch (68) highlighted some of the hazards of group discussions. She, for instance, described highly disturbed or manipulative parents who preclude group cohensiveness and identification, and inexperienced parents whose anxieties about their children mounted as they listened to other parents dramatic accounts of their childrens crises. The parents in Mattsson and Agle s group (83), for instance, nearly exclusively vented common hardships, at times sounding like "horror stories during their first meetings. Family therapy as tried successfully in families with an asthmatic child (73) is perhaps a better alternative to group therapy for parents whose children have a progressive disease such as CF and where the individual childrens medical condition may vary considerably Here too, however the greatest precautions must be taken not to destroy those modes of defense that serve the parents and the child well in their strivings to cope.

Four couples were divorced, 3 of them blaming CF The incidence of divorced couples in this study is, however slightly lower than the national mean. It may be that the CF child has been falsely blamed. Kollberg (63) did not find a hightened divorce rate among the Swedish CF families, fin- hich contrast to the investigations of Lawler al. (71) and of Dennings et al. (24) who found much higher incidences among their CF material, and of Jordan (49) who found a higher rate of disrupted marriages in families with handicapped children in general. The social structure of the different countries may explain these diverging findings, e.g. that the Swedish Health Insurance system prevents families from suffering financially as much as do families in various other countries (108).

Treatment

The tendency to give more treatment to a sicker child is clear The "dip" for the children with a mild medical condition is, however striking. One possible explanation for this might be that some of these children had a mild condition because they received too little treatment and that they would be in excellent condition with more care.

The mothers were the chief administrators of therapy which must be termed natural as most of the mothers had no or little work outside the home (80 %) while nearly all fathers were fulltime employed. The amount of help the fathers gave was not related to the amount of therapy the child received or to the medical condition of the child. Help by the fathers was given only slightly more if there were two CF children in the family If help was not received in giving therapy it was usually not received either in other chores involved with CF for example the cleaning of medical devices or administering drugs. In this context it must be pointed out that the child who is used to receiving therapy from the mother often is unwilling to have the father give therapy as the father often is unskilled in a way which the child may perceive as painful. It is, however highly desirable to prevent this "viscious circle The father as well as the mother should be well trained in giving the child therapy not only so that the father may unburden the mother but also as a source for furthering a better father-child contact. Remarkable is that 19 fathers never have tried to administer therapy and 3 have never even watched their wives treating their child.

It would be desirable if physicians treating CF children could be sensitive for the daily home care of the child. This side of the total management should, not only once, be discussed with both parents simultaneously

When the CF child grows older rebelliousness, depression and denial are frequently found. These reactions, according to Dennings et al. (24) should, rather than being interpreted as psychopathological, be viewed as adaptations to the disease and should be treated as such. However the need to be normal may very often, according to these authors, move the patient away from the optimal treatment program. Treatment ought therefore to be seen by the patient, as soon he is old enough, as a requirement to be normal—as something which he does to live well and to validitate himself as a person, rather than as an intrusion that demands, stigmatizes and controls.

The child's experience of his illness according to the mother Parent-child communication

The effect of parental, and especially maternal feed-back on the child's experience of his illness is of outmost importance (79 87), and can clarly be seen in many of the cases here reported. If parents think and show that the illness is a dreadful misfortune, the child will be prone to think the same. If the parents are bitter the child will be bitter if the parents often show pity the child will pity itself. If they are worried the child will be worried. Parents, on the other hand, who have learnt to take their child's illness naturally as an important part of their child, but certainly not the most important part, tended to have children who accepted their illness in a more natural way

The importance of early parent-child communication about CF cannot be enough stressed. The block in communication in several families with school- and teenage children may be, at least partly due to the mothers' own intense anxiety inhibiting her to encourage or accept the child's expression of its feelings. Glaser (35) has reported similar findings in mothers of children with rheumatic fever Only very few mothers could report the child's own expression of its fears. Bernstein reports that the questions of children with muscular dystrophy regarding prognosis evoke parental guilt feelings which are manifested in psychophysiological symptoms. Glaser et al. (34) found that mothers of children with cardiac disease could not report their childrens feelings of their fears. One third of the parents in McCollum and Gibsons study (86) of CF families had never discussed the issue of CF with their schoolage CF children. These parents recounted their fear that any communication with their child about its disease would result in direct questions about its possible death, a discussion with which they would be unable to deal. In Cytryn s et al. (23) study of CF families nearly all parents were unable or unwilling to talk with the child of its feelings. Boyle et al. (12), in their investigation of CF adolescents and young adults reported that only 20 % of the families encouraged their children to talk about CF In families where concern over CF could be aired, the patients tended to be more accepting of their difference from others. They seemed more comfortable with themselves and with others. Those patients whose parents discouraged discussions of the illness tended to display a sense of inferiority and showed marked hostility on projective testing, directed at the parents and at themselves. It was also clear from the testing that the patients were preoccupied with thoughts of their disease. Any attempt, however to consider the future made them so fearful that they would go to great lengths to avoid discussing their problems. Many of them claimed only to know the name Cystic Fibrosis although they had had their illness discussed with them by their doctor

The expression of anxious, sad and angry feelings at times and of confidence and guarded optimism during periods of clinical quiescence is characteristic of a well adapted child with chronic illness (81) and was, in this study reported by mothers of children in all 5 medical conditions. It is the child's *right* to be allowed to express these feelings, and the medical team can, and must, assist the ill child, starting early in the child's life, by encouraging it to ask questions and verbalize its feelings. The physician must be sensitive to this very important aspect of the care of the child and help the parents and the child in a constructive manner The earlier the child can start verbalizing his feelings instead of acting upon them, the better are his chances of a good adaptation.

The child's social position among peers as rated by the child's mother teacher and the author The teachers assessment of the child at school.

The mothers of children in excellent and mild condition tended to rate their children's social position among peers more adequately than those of children in more severe conditions. The latter mothers tended to overestimate the social position in comparison to the author's impression. The teachers, on the other hand, had a distinct tendency to rate average" often judging the child's social position as better than did both the author and the mother Most teachers stated that the illness was hardly noticed at school. If

deviated it was only physically This was also the statement of three teachers whose pupils died shortly after the teachers had answered the questionnaire. The teachers ratings may be true, but the "average" rating given by most teachers, can also be due to the current disinclination to grade children in any way in the Swedish schools. The teachers may be afraid that their answers will constitute a drawback for the child. However the *findings are also in accordance with those of* Rodgers et al. (102) who found that questionnaires to teachers added little to the overall assessment of the child at best it merely substantiated the findings of parent interviews. Werry (118) has noted that teacher's ratings have high validity on aggressive and acted out behaviour but are less accurate at detecting more subtle forms of maladjustment, particularly internalized neurotic conflicts and withdrawn behaviour which were the expected findings here. The opinion of the teachers may have been different if the questionnaire had been given orally either by telephone or personally

Level of aspiration

As a group, the mother's level of aspiration for their children *seems to be adequate with* consideration to the scale bias, except for the social aspiration" where the mothers of severely ill children seem to surrender to wishful thinking. Wishful thinking for "profession is difficult. *Nearly all employers in Sweden require a health-*certificate from a person applying for a permanent post, and thus, together with the new employment laws (104) are realities which cannot be overlooked. Every employer who accepts an applicant today shoulders a protracted responsibility for this person. In reality this means that many employers hesitate before they accept an applicant who is not in the best of health, a fact which the mothers appear to be aware of.

"Economically" follows "profession" to a certain degree, but is somewhat compensated by the Swedish social security laws. One mother whose son was in excellent medical condition, answered that profession and economy were no problem since the handicapped are so well taken care of in Sweden that her son would never have to bother with a profession.

Healthy siblings

The problems of the healthy siblings have only been briefly dealt with in this study Significant problems are present in many of these children as has also been found by other investigators. In Allen et al's. study of CF families (4) one third of the mothers with unaffected children reported that they had one or two healthy children whose overall behaviour was a worry to them. Soiling, stealing, firelightning and undiagnosed recurring abdominal pain were some of the problems noted. Kahn et al. (51) has noted behavioural changes and problems as a result of jealousy and lack of parental attention in siblings of children with kidney transplantation, and the same thing has been noted in siblings of children with hemophilia (2), Tay Sach s disease (53), mental retardation (11 80) and handicapped children in general (97). Pozanski (97) has frequently seen siblings of handicapped children with emotional problems more severe than those of the handicapped child itself This last finding was true in at least 2 families in the present study

It thus seems as if healthy siblings of chronically ill children are very much at risk. Here again the physician can assist greatly by pointing out dangers before they occur thus trying to prevent pathological patterns of behaviour When these have already occurred, Mandelbaum and Wheeler (80) have noted that "efforts to call attention to the neglected needs of siblings usually arouse anger and deep resentment in the parents The physician should try to assess whether the siblings are receiving needed parental love and attention as well as acceptance of their frequent feelings of anxiety and resentment towards their sick brother or sister Here again the above suggested extention of the physician in the form of a visiting, well trained medical social worker could be of immense value.

*Anxiety concerning future marriage and child-*bearing has been noted among siblings of mentally

retarded children (29). Worries of this kind surely exist in siblings of ill children with hereditary diseases and handicaps of other kinds and may be a good reason for the pediatrician to invite siblings in for a discussion when they reach adolescence. Adolescents need to be able to talk with someone about these feelings (29) and are often not able to discuss such issues with their parents.

Meyerowitz and Kaplan (89) found that the presence of healthy siblings who were aware of their CF sibling's diagnosis was a significant source of stress for the parents. It was assumed that the source of such stress was anxiety about the possible traumatic effect of the knowledge of the negative prognosis upon their non-CF children as has been *found* in familial studies of leukemia and mental retardation. This cause of stress was, however not mentioned by any of the parents in this study

Mothers work

Having a child with CF makes it difficult for a mother to work outside the home and this is true even if the child is in a good medical condition. Treatment must be given on a daily basis and when the child is infected its care requires the presence of a person well trained in administering its therapy

Meyerowitz and Kaplan (89) have noted that mothers who perceived great difficulties following the diagnosis were significantly more likely to express a desire to escape an intolerable situation by going to work than mothers who did not so perceive the situation. Of the 6 mothers who had fulltime employment in this study 5 had experienced such difficulties.

Isolation and overprotection

A danger with every sick child and in particular with every chronically sick child is overprotection from its adult surroundings. As one 16 year old hemophilic boy put it. "Don't worry about the kids, Doc, but help the parents with their worries so they can treat us like normal children! -(84)

Any child being raised by oversolic-trolling and fearful parents will sense the parental anxiousness for his vulnerability (40). This kind of parental care will deepen the child's feelings of insecurity and may cause him to become emotionally handicapped even before a physical handicap is noticeable. The parents need help and instruction in how to develop in their child an increasing responsibility for self-care and protection.

Many mothers report feelings of isolation due to CF and it is obvious and understandable that isolation is a fact for the majority of these parents. Assistance in the home must be provided through physiotherapists, homehelpers" etc. for parents who are isolated on account of too much work with CF In other families, however isolation should not have to be so profound, for instance in families with one CF child in excellent condition. It would be very helpful if the physician treating the CF child could be "open even for this side of the total management and help the parents towards more realistic precautions.

Nocturnal enuresis and sleeping difficulties

A variety of age limits for attaining nocturnal bladder control is found in the litterature. Braithwaite (13) states that 95 % of 5 year old children, Oppel (91) that 91 % of 6 year old children and Hallgren (41) that 92 % of the boys and 96 % of the girls at 7 years of age are dry at night. Klackenberg (57) and Peckham (96) in accordance with Hallgren report a higher incidence of nocturnal enuresis among boys than among girls. Secondary enuresis, which occurs after a sufficiently long period of demonstrable control, is always a deviation from a normal state (57) and is often caused by psychologic factors (52). Girls are very little in evidence of secondary enuresis at any frequency level according to Klackenberg.

The incidence of nocturnal enuresis among CF school-children in this study is much higher than was found in a random Swedish population (57). This is in line with McCollum and Gibson s findings (86). The most probable explanation of this deviation is that it is secondary to the psychologic burden of having CF Carne (18) reports t findings among diabetic school childre-

indisputable. A different approach to the question of employment would be to let the state keep employers indemnified through an insurance that would pay the eventual loss caused by chronic illness among employees. This would help strenghten the selfdignity and reliance of the young handicapped person, for whom it is so important that he posess a high level of self esteem as well as ingenuity fortitude and courage, to balance all the difficulties, physical as well as psychological, that he will be bound to meet in the wake of his life.

VII. EPILOGUE

In the process of growing up, children, healthy as well as ill, unconsciously form psychological defenses in their efforts to cope with the stresses and strains of life. Readjustments of inner needs to outer realities must be made and this applies even more so to the chronically ill child. The way in which the child unconsciously makes these readjustments determine the patterns of his developing personality. Parents here yield an extremely significant influence. They are intimately involved in the creation of their child's formative experiences in ways of which they are often unaware—as a matter of fact, the most important psychological interchanges between parent and child are more often covert than overt.

The situation for the parents of a CF child, as well as for the parents of children with other chronic disorders, is extremely difficult. They are urged to treat their child like a normal, healthy child, but many times a day they are reminded that their child is not healthy and this prevents them from seeing their child as a whole. Very often they feel that they in some way must compensate their child for everything he has to go through by doing everything for him or through letting him have his own way. In doing this they do not realize that they prevent the child from making those readjustments and from forming those defenses which the child will need and must have in his future life and which will maximize his potential for living within the framework of the limitations imposed by his disability.

The life expectancy for children with CF is increasing for every year that passes. Every effort must be made to make the longer life that the child and all who care for him may hopefully look forward to, as rich and as meaningful as possible. In the words "potential for living" lies a great challenge to all of us.

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Cecilia Falkman

X. APPENDICES

Appendix 1

Questions in the interviews

General

1 Name and date of birth of parents, CF child and siblings. Does or did any of the siblings have CF? Date in case of death of CF sibling.

Pre-diagnostic phase

2. Did the parents know about CF before the child participating in the study (henceforth "the child") was born?
   a) yes, other CF children in the family
   b) yes, other CF children in the kindred but not in the immediate family
   c) yes, through information in newspapers, magazines, T V etc.
   d) no

3 How long had the parents been married or lived together before the child was born?

4 When did the parents start to suspect that something was seriously wrong with their child?
   Why?

5 When was the first visit to a doctor made because of these suspicions?
   a) the child was retained at the hospital after birth
   b) at once or within one month
   c) within 2–5 months
   d) after more than 5 months

6 About how many different visits to doctors did the parents make with their child from the time they started to suspect something was wrong till the diagnosis was made?

7 Did the parents on their own initiative visit different physicians to obtain help?
   a) yes
   b) no

8 If yes, what specialities did these doctors have?
   a) pediatrician
   b) general practioneer
   c) medical county officer
   d) ear-nose-throat specialist
   e) homoeopathist
   f) other category
   g) 2 or more of the above categories

9 Where the parents content with possibly incorrect diagnoses?
   a) yes
   b) no
   c) no incorrect diagnoses

10 Did the parents feel that they received understanding for their fears from the physician(s) during the time between arousal of suspicion and the diagnosis? If yes, in what way if not in what way? Specification.
   a) yes
   b) the parents were not worried or did not let their fears show
   c) the CF child not the first CF child in the family
   d) no

11 Did the child have any troubles with its stools during the period before the diagnosis?
   a) no special difficulties
   b) difficulties. Specification
   c) great difficulties. Specification
   d) the child was hospitalized during the whole period

12. Were there any feeding problems during this period? In what way? Specification

13 Are there currently any feeding problems In what way? Specification

46 Was this doctor positive or negative in his/her attitude towards further children in the family?
a) positive
b) neutral
c) negative

47 Have the parents had further children after their first CF child?

48 If so were the parents aware of the risk of further CF children?
a) yes
b) no no genetic information
c) no incorrect genetic information
d) CF child nr 1 still undiagnosed

49 If the parents were aware of the risks, how did they reason when deciding to have further children?
a) wanted to take the chance
b) the child was a "mistake"
c) took for granted that the child would be healthy (1 4)
d) did not consider the illness severe enough to refrain from further children
e) other reasoning – Specification

50 How do the parents think their child s current physical condition is, compared to healthy peers?
a) the same
b) nearly the same
c) somewhat weaker
d) much weaker
e) cannot be compared

* 51 Can the parents compare their child s physical health today to how it was one year ago?

52. To how it was 2 years ago?

53 To how it was 3 years ago?

54 What are the parent's level of aspiration for the future for their child, physically if compared to healthy peers?

55 The parent s level of aspiration socially?

56 The parent s level of aspiration economically?

57 The parent's level of aspiration professionally?

58 How extensive is the treatment of the child when not ill or infected?
a) no treatment
b) 1–30 min/day
c) 31–60 min/day
d) 1–2 hours/day
e) 2–4 hours/day

59 How extensive is the treatment of the child when ill or infected?
a) no treatment
b) 1–30 min/day
c) 31–60 min/day
d) 1–2 hours/day
e) 2–4 hours/day
f) 4–6 hours/day
g) more than 10 hours/day

60 How do the parents experience the treat ment of their child?
a) no trouble, as part of the daily routine
b) as a rule without trouble
c) as a burden

61 When do the parents experience it as most stressful to give therapy or treatment?
a) no difference
b) in the morning
c) *in the afternoon*
d) in the evening
e) when on holidays
f) week-ends
g) little or no therapy
h) the child gives itself what little therapy it gets

62. Is there any trouble with medication? Why? In what way?

63 Is there any trouble with the mist-tent? In what way?

* 64 Do the parents experience the special diet as troublesome? In what way?

65 Can the child (sometimes) take care of his/her own medication?
a) yes
b) can, but is not allowed to
c) no

66 To what extent does the father help with the treatment?

67 To what extent does the father help in the care of apparatus?

68. To what extent does the father help in the contact with physicians?

69 Does the father help with something else in order to facilitate the mother s CF-work? Specification.

70. How does, according to the parents, the child experience its illness?
   a) not conscious
   b) naturally
   c) suffers and is embarrassed to a certain extent
   d) suffers very much

71 How does, according to the parents, the child experience treatment?
   a) no problem
   b) difficult occasionally
   c) difficult
   d) very little or no treatment

72. How does, according to the parents, the child experience medication?
   a) no problem
   b) problems. Specification

73 What do the parents do when the child does not co-operate during treatment?
   a) skip treatment (that session)
   b) wait till later
   c) pay no heed to the unco-operativness of the child
   d) the child always co-operates

74 At what age did the child start to be aware of its illness?
   How did the parents notice?

75 At what age did the child start asking question about CF?

76. Can the parents give satisfactory answer to their child's questions about CF?
   a) always
   b) most of the time
   c) hardly ever
   d) never

77 Do the parents feel unprepared when the questions come about?
   a) always
   b) most of the time
   c) hardly ever
   d) never

78 How do the parents answer their child's questions about CF?
   a) very truthfully
   b) truthfully but paraphrased
   c) avoidingly
   d) no questions

79 Is the child natural in his attitude to CF when with peers or is the child unhappy or embarrassed?
   a) natural
   b) not natural, unhappy pained
   c) not yet aware of CF

80 What "kind of children does the child prefer to be with?
   Ex.
   a) children of the same age
   b) older children
   c) tough children
   d) younger shy or calm children
   e) children of the opposite sex
   f) other children with illnesses or problems
   g) no preferences

81 How would the parents rate their child s social position among peers?
   a) leader
   b) somewhat more foreward than average
   c) average
   d) somewhat lonelier than average
   e) isolated
   f) picked upon (Sw "hack-kyckling")

82. Do the parents feel that the child in some way tries to compensate for physical weakness?
   a) yes. Specification
   b) no
   c) the child is not physically weak

83 Does the child suffer from sleeping difficulties?
   Specification

84 Does the child suffer from enuresis or nocturnal enuresis?
   Specification.

85 How does the child experience being an in-patient in the hospital? (When not acutely severaly ill)
   a) no problem
   b) no greater problem
   c) difficult

86. How does the mother experience the child being an in-patient in the hospital? (When not acutely severaly ill)

a) restful not to have to give the daily treat ment
b) no problem
c) no greater problem
d) difficult

87 Can the parents mutually and openly discuss CF and all the problems involved?
a) yes
b) yes, the parents can but do not wish to
c) no
Specification

• 88. Have the parents told their own parents about CF? How have these reacted?
a) yes. Reaction.
b) no Why?

89 Have the parents told other relatives about CF and how have these reacted?
a) yes. Reaction.
b) no Why?

• 90. Have the parents told their friends about CF?
a) yes. Reaction.
b) no Why?

• 91 Do the parents tell more peripheral aquaintances about CF?
a) yes
b) sometimes
c) no

2. Do the parents tell strangers, for example on the playground, about CF?
a) yes
b) yes, when the child coughs
c) no

93 Are the parents agreed upon how much to tell others about CF?
a) yes
b) parents do not agree but there is no conflict
c) parents do not agree – conflict. Specification

94 Do the parents feel that they have enough time for the CF child's healthy siblings?
a) yes
b) no Specification

95 Are there any problems with the healthy siblings?
a) yes
b) no Specification

96. Do the parents easily give in to their child?
a) yes. In what way?
b) try unsuccessfully not to Specification
c) no

97 Do the parents feel isolated on account of CF?
a) yes, on account of the risk of infections
b) yes, because the child is too ill to allow the parents to leave it
c) yes, because the parents do not want others to know that the child eats pills, or uses apparatuses or sleeps in mist-tent
d) yes, difficult to find baby-sitters or do not trust baby sitters
e) yes, other reasons. Specification
f) no

98 Can the parents, in spite of all difficulties, see something positive that CF has brought to the family?
a) yes. Specification
b) no

99 Would the mother like to work outside the home? If she would but does not on account of CF in her child, how does she feel about this?
a) would not like to work outside the home
b) would like to work outside the home but feels no bitterness
c) would like to work outside the home and feels bitter
d) works part-day but would like to work whole-day
e) works whole day

100 How do the parents experience TV programs about CF?
a) neutral – positive
b) negative
c) very negative
d) do not see them
e) the parents have different opinions Specification

101 Would the parents like to have contanct with other CF families?
a) Why?
b) Why not?

102. How has the mother felt about having this interview?
Specification

Appendix II

The teacher s questionnaire

The Swedish Association for Cystic Fibrosis has, for some years, been conducting an extensive investigation concerning all aspects of Cystic Fibrosis. One of these aspects is the psychological side of the illness—an aspect of the total disease to which, up till now very little attention has been paid. The illness can, quite naturally often cause severe emotional and psychological problems for not only the child but for his/her parents and eventual healthy siblings as well. In order to try to assess the kind and the magnitude of psychological problems the illness poses on the child and his family I have visited more than one third of the families in Sweden who have one or more children with Cystic Fibrosis. The CF child in your class belongs to one of these families and the parents have given me permission to contact you with this questionnaire. To get the child's teacher's objective view of his/her behaviour and methods of adaptation is very valuable and I therefore ask for your help in answering the questionnaire. I am, of course, very thankful for any additional information you may have in respect to how the child copes with his/her illness in the total school situation.

Thank you very much for your co-operation

/Cecilia Falkman/
psychologist, board member of RfCP

Name of the child

Class

1 How would you estimate the child s physical size in relation to his/her classmates?
   a) Bigger than average
   b) Average
   c) Somewhat smaller than average
   d) Among the smallest in the class
   e) Smallest in the class

2. How much physical strength does the child have in comparison to his/her classmates?
   a) More than the classmates
   b) Average
   c) Somewhat less than the classmates
   d) Considerably less than the classmates

3 If the child is physically inferior to his/her classmates, how does he/she react to not being able to do as much as others?
   a) Is not conscious thereof or does not seem to think about it
   b) Tries to participate anyway
   c) Withdraws from the activities of peers

4 How do the classmates react if the child is physically inferior and does not have the strength to participate with them on equal terms?
   a) Pretend they don t notice
   b) Are considerate and let the child participate
   c) Are irritated and would rather not have the child participate

5 Is it your impression that the child if physically inferior in some way tries to compensate for this?
   a) yes
   b) no
   If yes, in what way?

6 If the child was in your class already last year can you try to rate how it on the whole is, physically compared to last year?

a) Better
b) No change
c) Worse

7 What rate of absence does the child have com pared to his/her classmates?
a) Much greater
b) Greater
c) The same
d) Smaller

8 How would you rate the child s social position among peers?
a) Leader
b) Somewhat more foreward than average
c) Average
d) Somewhat lonelier than average
e) Isolated
f) Picked upon (Sw "hack kyckling")

9 What "kind" of children does the child prefer to be with? Ex. older younger smaller tough, shy children with the same interests, another child with a handicap etc.

10. Do you consider the child overprotected from the home?
a) Yes. In what way?
b) No

Does the child crave much attention?

	From its mother	From you
a) Yes		
b) No		

	From peers
a) Yes	
b) No	

12 Has the mother informed about Cystic Fibrosis?

	You	Classmates	School lunch personnel
a) Yes			
b) No			

13 How much contact do you have with the child s mother?
a) More than with other mothers
b) As much as with other mothers
c) Less than with other mothers

14 Does the child speak of his/her illness?

	With you	With classmates
a) Often		
b) Sometimes		
c) Never		

15 Does the child ever blame failures of different kinds on CF?
a) Often
b) Sometimes
c) Never
If a) or b), what kind of failures are these?

16 Does the child in your opinion suffer or is it ashamed of

	Yes
a) Its small size	
b) Its cough	
c) Going to the toilet in school	
d) Showing that it eats drugs	

	Somewhat
a) Its small size	
b) Its cough	
c) Going to the toilet in school	
d) Showing that it eats drugs	

No

a) Its small size

b) Its cough

c) Going to the toilet in school

d) Showing that it eats drugs

17 Does the child itself take the responsibility for his/her medication in connection with the school lunch?
a) Yes
b) No

18. Are any special arrangements made for the child in connection with the school lunch?
a) The child does not eat lunch in school on account of its illness
b) The child takes his/her drugs in secret
c) The child does not have lunch at the same time as his/her classmates
d) Some other arrangement?
e) No

19 Does the child have any curricular difficulties?
a) Yes, difficulties with.
b) No

20. Does the child receive extra help with any subject?
a) Yes, with.
b) No

21 Does the child participate in

Yes Most of the time

a) Gym

b) Field days

c) School outings

Sometimes Seldom No

a) Gym

b) Field days

c) School outings

22. Does the child, in your opinion, in any way "use" his/her illness for example through playing tired in order not to have to participate in something it dislikes?
a) Yes, sometimes, in that it.
b) Yes, often in that it.
c) No, never

23 Does it ever happen that the parents blame a failure which in your opinion has nothing to do with the child's illness, on the illness?
a) Yes. Specification
b) No

Thank you again for your co-operation

a) Better
b) No change
c) Worse

7 What rate of absence does the child have compared to his/her classmates?
a) Much greater
b) Greater
c) The same
d) Smaller

8 How would you rate the child's social position among peers?
a) Leader
b) Somewhat more foreward than average
c) Average
d) Somewhat lonelier than average
e) Isolated
f) Picked upon (Sw· "hack kyckling")

9 What "kind" of children does the child prefer to be with? Ex. older younger smaller tough, shy children with the same interests, another child with a handicap etc

10. Do you consider the child overprotected from the home?
a) Yes. In what way?
b) No

11 Does the child crave much attention?

From its mother From you

a) Yes

b) No

From peers

a) Yes

b) No

12. Has the mother informed about Cystic Fibrosis?

You Classmates

a) Yes

b) No

School lunch personnel

a) Yes

b) No

13 How much contact do you have with the child s mother?
a) More than with other mothers
b) As much as with other mothers
c) Less than with other mothers

14 Does the child speak of his/her illness?

With you With classmates

a) Often

b) Sometimes

c) Never

15 Does the child ever blame failures of different kinds on CF?
a) Often
b) Sometimes
c) Never
If a) or b), what kind of failures are these?

16 Does the child, in your opinion, suffer or is it ashamed of

Yes

a) Its small size

b) Its cough

c) Going to the toilet in school

d) Showing that it eats drugs

Somewhat

a) Its small size

b) Its cough

c) Going to the toilet in school

d) Showing that it eats drugs

Appendix V

Chi Square values of the HFD test

APPENDIX V Chi Squar values of the HFD test

Emotional indicators	CF/Dnb.	CF/Clin.	CT/Well adj.
Poor integration	0.001	0.047	6.391
Shading of face	2.713	1.416	6.391
Shading of body	1.423	0.140	2.496
Shading of hands	0.118	0.003	1.287
Asymmetry	1.236	1.758	10.107
Slanting figure	0.024	0.041	6.391
Tiny figure	10.539**	3.042	0.077
Big figure	0.380	1.312	12.027**
Transparencies	3.945	0.047	3.800
Tiny head	0.067	0.001	0.077
Crossed eyes	0.000	0.000	0.000
Teeth	4.801	0.326	1.416
Short arms	4.717	0.077	5.180
Long arms	4.801	0.094	3.996
Arms clinging to body	7.334**	1.041	0.119
Big hands	0.067	0.003	1.287
Hands cut off	1.363	0.021	2.503
Legs together	2.658	0.000	0.001
Genitals	0.118	0.001	1.287
Monster	0.118	0.000	0.236
Three figures	0.118	0.048	1.287
Clouds	0.118	0.108	0.236
No eyes	0.118	0.001	1.287
No nose	2.402	0.482	3.800
No mouth	0.067	0.048	1.287
No body	0.067	0.100	0.077
No arms	0.022	1.041	0.000
No legs	0.015	2.886	2.886
No feet	0.151	0.094	1.277
No neck	0.347	1.185	0.077

Appendix VI

Cystic Fibrosis in Sweden (1977)

Hans Kollberg

General background

The Swedish system for medical care is very tightly organized and centralized. The country is divided into 7 hospital regions, each of them containing a regional hospital capable of serving about one million people and equipped with clinics for certain highly specialized fields. The regional hospitals are located in the towns of Umeå, Uppsala, Stockholm, Örebro, Linköping, Gothenburg and Lund. So far there are centers for cystic fibrosis in Umeå, Uppsala, Stockholm, Gothenburg and Lund. To each region a different number of counties belong. In every county there is at least one central hospital with a pediatric clinic, which always has the possibility to take care of CF-patients.

The Swedish compulsory sick insurance (70, 108) is constructed to give everyone with an illness or a handicap the possibility of care without economical limitations. The insurance gives.

Free hospital care for in-patients,
Out-patient visits—including X rays, laboratory services etc—to a very low fee (about US$ 3.00)
Subscribed expenses for travels to doctors and hospitals
Subscription of drugs on prescriptions (all drugs for a single occasion—even if covering several months—cost a max. of US$ 4.00)
Free drugs for certain chronical diseases
Free maternity care
Free well-baby clinics
Free "four-year control"
Free health care at school
Free dental service in childhood and during pregnancy
Free check ups for certain diseases (such as tuberculosis, veneral diseases, malignancy in female genital tract)
Sickness cash benefit
Certain additional aids to handicapped and crippled

Among the additional aids to handicapped one may mention a care allowance for parents who take care of a CF-child, and if the child is particularly sick, additional allowance for sick-care at home. Mist tents and inhalators are, usually bought by the counties and lent to the patients as long as they need the equipment. Some counties or communities give additional help, for example, free physical therapy including training of the parents and free transportation to and from school if needed.

All children have a garanteed possibility of education.

Material and methods

Information about all patients in Sweden has been collected in the following ways.

a) Questionnaires to all pediatric clinics about known CF-patients who were living 1 1 1968 or later was sent out 1970, and has been followed up 1972, 1973, 1974 and 1976. All pediatric clinics have cooperated well.
b) The completeliness of the register has been checked by
   1) control of all prescriptions of pancreatic enzymes during a three months period in 1970
   2) control of the central register at "Riksförsäkringsverket" of parents receiving care allowances due to a CF-child in 1970

3) control of the diagnostic registrations in the region of Stockholm 1972
4) control of the register of sold mist-tent equipment with AB Stille Werner (the only company which sold this equipment before 1975)
5) following the register of members in the Swedish Association of CF

The criteria for the diagnosis of CF have been.

a) Pathological sweat tests (mainly done by the method of Gibson & Cooke (33) *and* a minimum of one of the cardinal symtoms of chronic lung disease, malabsorption or meconium ileus.
b) meconium ileus with death before sweat-test has been done but with typical post mortem findings of CF In addition 17 patients were accepted to enter the first year though a proper sweat-test had not been performed. They all had typical clinical manifestations with chronic lung disease, chronic sinusitis and malabsorbation and absence of trypsin or chymotrypsin in duodenal fluid or in faeces or (one) rectal prolapse.

The information about diagnosis has been taken from the patient s hospital records.

The information about degree of sickness, treat ment and social circumstances has been taken from a questionnaire to the parents which was sent to the parents of all 132 known CF-patients in 1970 and arwered by 122. All medical parameters were estimated by the author and all social parameters by one social worker

Follow up studies have been made by the author in collaboration with a social worker of the Swedish CF Association, by repeated contacts with the families, their local doctors and their local social workers. Emphasis has hereby been made on those families who have been known to have special problems.

Incidence life expectancy

All patients with a known diagnosis of CF have been registrated in Sweden since 1968 (Table XI).

Table XI Number of CF-patients in Sweden 1968–1976

Year	1.1	1.1 – 31 12 new	dead	31 12
1968	116	14	7	123
1969	123	19	13	129
1970	129	19	6	142
1971	142	15	7	150
1972	150	20	11	159
1973	159	14	5	168
1974	168	20	9	179
1975	179	16	7	188
1976	188	18	9	197

The number of patients has increased constantly Since the number of new diagnosed CF patients has been rather constant, this increase must be due to an increased survivorship. The life expectancy (calculated with life table studies of mortality by W.J Warrwick (115)) has in fact improved considerably from 7,5 years to 13[1] years of age during the period 1968–1976 and the age distribution and median age is also rising.

The incidence has been calculated on the age group with the highest amount of patients (1969 3–4 year olds and 1972 7–8 year olds) and corrected for children who have died earlier and for children who still might be undiagnosed. This gave an incidence of 1.3000 newborns (63). In a true randomly selected screening series of 8.830 newborns the expected number of 3 new cases were found. In Sweden, where about 100.000 children are born each year this should mean around 33 new CF-children per year In comparison to Table XI, this also indicates that more than 1/3 of all CF-children will never be diagnosed, which is in concordance with the values in USA estimated by W.J Warwick (116).

Treatment

In the spring of 1977 all patients are outpatients living mainly in families and treated by their parents, six of the oldest are living on their ... four of them with partners who help them with ... treatment. The pediatrician at the nearest ... is, generally the one who has the ...

sibility for the management of the treatment, but during the last 10 years it has been more and more common to have a CF-specialist from the region hospital supervise the therapy—today about 60 % are regularly and additional 25 % are sporadically seen at the region hospitals.

The treatment of the lungs has been intensified during the last decade. The mucus liquifying measures—mist tents and short term inhalations started in the late 60's and since the beginning of the 70 s about 80 % of the patients have slept in mist tents or have had inhalations or both on a regular or intermittent basis. Simultaneously the importance of physical therapy has been stressed and today more than 90 % of the patients get physical therapy at least when they are infected. The physical therapy is generally given by the parents—mainly the mothers—but more and more families get intermittent help from licensed physical therapists. Some patients, mainly those in an excellent or mild condition, do not get regular physical therapy but are recommended a high physical activity to help to keep their lungs in a good condition.

A contradictory point of treatment in Sweden has been the policy to administer antibiotic treatment. In 1970, 44 patients had antibiotics continously 33 regularly intermittent, 26 seldom and 19 never Today however the trend is to give all CF-patients antibiotics liberally whenever they are infected, but not prophylactically

The nutritive treatment has been rather uniform throughout the country and throughout the decade. The diet is recommended to provide increased amounts of calories and proteins as needed to satisfy the requirements for growth and development and with a variable reduction in fat. A strict diet is very seldom needed. Nearly all patients get substitution for pancreatic enzymes at meals, and extra vitamins.

The comprehensive programs for management of CF have during the decade been more unified throughout the country thanks to intensive information both to physicians (58, 64) and to parents (59 60, 61).

Economic and Social aspects

The biggest burden to the economy of the CF-families was—according to the study 1970—the fact that the mothers could not work outside home. Extra costs for the treatment—except those covered by the social security—varied very much.
1/3 had nearly no extra costs
1/3 aroud $ 200—250 per year
1/3 $ 200—2000 per year

It is, however probable that there were additional extra hidden costs for water electricity laundry etc. Economical help was 1970 given to about 70 % of the families mainly as care allowances (63). At the 1970 inventation it was found that more than half of the CF-familes needed help by a social worker Measures included Increased periodic care allowances, better housing and support to the rent, help to a car or to communal transportation service, getting a phone, help with cost for drugs or equipment, help by a physical therapist or a social home assistant, help to break social isolation, help to recreation (CF camps, journeys in Sweden or abroad), help to find a job for the older CF-patients and better medical follow-ups. At that invention 60 CF families were considered to have a good, 42 a fair and 12 a poor economical state (63).

During the 70's the possibilities for the CF-families to get an adequate help from the social security has improved considerably thanks to the Swedish Association for CF (RfCF). This has employed a half-time social worker who has contacted all families with a new-diagnosed CF-child and given information about the different possibilities for social aid in the treatment. A continous contact has been kept with those families, which have been considered to need it, and the CF-families have also had the possibility to take a contact whenever they need it.

School attendance for CF-children is troublesome. In 1970 2/3 were regularly away so much that they needed extra support for teaching but only a few got it. Many had problems to have time to do the treatment with inhalations and

physical therapy before the school start in the morning, but only exceptionally was this taken into consideration on the school schedule. No arrangements were made for those CF-children, who had problems in physical training or on excursions. No occupational advise with special CF aspects was given before 1974 but since then all older CF-patients have got individual advise by the social worker at RfCF

Also all other problems of older teen agers and of young adults with CF were unheeded until recently when RfCF started a special service for them with sexual and genetic counselling, information about the disease and its treatment, help to be able to live on their own with or without a partner occupational advise and finding of a job. Still there are, however considerable difficulties on this field mainly because the lack of physical therapists to give home-treatment and the difficulty to get a job.

Psychological aspects

The psychological aspects of CF both for the patients and for the families were taken into consideration very little 1970. More than half of the patients had never had any contact with a social worker Most families felt isolated and did not know anyone else with the disease. There was practically no information about CF in the 60's. Thus the diagnosis was easily missed and the understanding from the environment of the problems for the patients and their families was nonexistant. There were no possibilities for the patients to leave the parents and—subsequently—no possibilities for the parents to have a recreation period for themselves.

As described, most patients now go to the same doctor and many of them regularly meet a specialist in CF Nearly all patients are now referred to a social worker at time of the diagnosis, and many have regular contact with the social worker of RfCF

More than half of the families now meet one or several times per year at meetings or other activities of RfCF The information has been intensive—booklets for doctors (58), physical therapists (60), teachers (62) and parents (61); pamphlets, articles in newspapers, films and TV programs for the public; and a regular journal from the RfCF (59) have appeared. Activities have been arranged by the RfCF in order to give the patients an opportunity to successively be more independent and in order to give the parents the opportunity of a recreation. These activities have included. recreation weeks for families, summer-camps for children, exchange journeys to the US, a teenagers-week in Italy with skiing in the mountains, individual advise for school-excursions, for confirmation-camps and for riding-camps, help to arrange physical therapy when moving from parents' home, help to get a job etc.

The Swedish Association for CF (RfCF)

RfCF was founded in August 1969 Its goal is to in every way combat the disease of CF and to help the patients with the disease. The rules of RfCF state, that the tasks of the Association are:

a) to give patients with CF support in the treatment and help them to adapt in the community
b) to inform about CF
c) to work for support to research in CF
d) to foster contacts with similar organizations in other countries.

RfCF has been working under hard economical conditions and has so far only had the possibility to employ a social worker on half time and a secretary The author has served as a medical consultant for the Association since its start.

Projections into the future

Today we still do not know the cause of CF and we do not have a definite cure. But research and experience have given us many hints how to manage with a good care of the patient with CF In Sweden, a program has been proposed for the treatment of CF which include suggestions for medical, psychological and social care (65).

Some of these suggestions are.

Medical Establishing of one or more CF centers with teams which are specially trained in the problems of CF an extended trial of screening for CF a special net of diagnostic possibilities b-

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Insulin in Juvenile Diabetes

Theory and Practice

EDITOR JOHNNY LUDVIGSSON

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LINKÖPING 1977

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The aim of this meeting was to bring together people working with both clinical and theoretical aspects of diabetes. While the clinical workers need to refresh their knowledge and to receive information about recent discoveries it is important for scientists to keep in contact with the practical problems in the management of diabetes the improvement of which should be the ultimate goal for diabetic research.

The idea of the symposium was met with enthusiasm from the participants and I want to thank all who contributed to its success. I am most grateful to all authors for a pleasant and fruitful cooperation.

I am especially indebted to my collaborators Professor Yngve Larsson and Dr Anders Häger who participated actively in the planning and arrangement of the symposium.

My sincere thanks are also due to secretary Helene Nordahl for her excellent work both with the practical arrangements of the meeting and for her skilful help with this supplement and to Professor David Lewis for supervising the English text.

This symposium was made possible through generous contributions from NOVO INDUSTRI AB and I should like to express my gratitude to NOVO for their support. Without their help the symposium could not have taken place.

The Editor

In the treatment of juvenile diabetes *insulin* remains *the* most important of the therapeutic tools necessary for adequate metabolic control Nevertheless, compared with the endogenous insulin secretion in the normal individual the injected insulin represents only a poor imitation of the physiological situation. During the past few years there has been a rapid development in this area of diabetes research. New knowledge is now accumulating which may lead to a breakthrough in this field with far-reaching implications for the practical management of diabetic patients The number of meetings symposia and workshops on diabetes which have taken place recently bears ample witness to this Frequent opportunities for workers in this field to meet and discuss common problems are obviously of great value for the development of diabetic research clinical as well as experimental Special attention should be given to the pediatric aspects of juvenile diabetes in such meetings which otherwise may easily become dominated by the many and naturally different problems of diabetes in the adult population. Thus it was the purpose of the present symposium the second of a series of meetings on diabetes emanating from our department, to throw light on some recent advances in the field of juvenile diabetes of special interest for pediatricians

It may be appropriate to identify the problem area by a definition of juvenile onset diabetes (JOD) By JOD we mean that particular type of insulin dependent diabetes mellitus in which clinical onset occurs before 20 years of age (growth-onset diabetes) It also includes the much smaller group of so-called maturity onset diabetes in young people (MODY)

The size of the problem is indicated by the results of a recent Swedish multi-center study [1] which showed a mean yearly incidence of JOD of 19 6 per 100 000 children 0–15 years of age and a mean prevalence of 1 3 per 1 000 children 0–15 years old This implies that there are about 350 new cases of JOD every year in Sweden and that by January 1976 there were about 2 500 diabetic children attending the clinics of the departments of pediatrics in this country

The title of this conference—the theory and practice of insulin in juvenile diabetes—is of course rather comprehensive, and cannot be covered completely Instead we have chosen to concentrate the discussions within the framework of the four sessions of the conference on some special problems of current interest, i.e problems related to the structure biochemistry and physiology of the islet organ the immunology of insulin the clinical use of insulin and some possible future changes in the therapeutic use of insulin in juvenile diabetes

I am glad that it was possible to organize this meeting, and I hope that the proceedings will be helpful to pediatricians and others who care for the growing population of children and young people with diabetes

Yngve Larsson

Sterky G Holmgren G Gustavsson, K H, Larsson Y Lundmark, K M Nilsson K. O Samuelsson G Thalme B and Wall, S The incidence of diabetes mellitus in Swedish children 1970–1975 Acta Paediatr Scand 1978 (in press).

ASPECTS OF THE STRUCTURE AND FUNCTION OF THE PANCREATIC B-CELL IN DIABETES MELLITUS

CLAES HELLERSTRÖM and ARNE ANDERSSON

From the Department of Histology University of Uppsala, Uppsala, S eden

The ability of the pancreatic B-cell to respond to hyperglycemia with insulin release is one of the key factors that determines the development, course and outcome of diabetes mellitus In a broad sense diabetogenic influences are continuously active in the organism and are normally balanced precisely by adjustments of the B-cell function. It is conceivable that two mechanisms are operative in this context namely a minute-by minute regulation of the insulin release from the individual B-cell and a more long-term adaptation involving changes in the total B-cell mass. It seems furthermore plausible that disturbances in either of these mechanisms may be of etiological significance for the manifestation of diabetes It is the purpose of this paper to review briefly the present state of knowledge regarding the effects of various diabetogeneic factors on the B-cell structure and function

ISLET MORPHOLOGY

Attempts to clarify the pathophysiology of the B-cell are complicated not only by the dispersion of the endocrine pancreas into a million or so islets of Langerhans (comprising in all only 1–2 per cent of the pancreatic parenchyma) but also by the fact that each islet contains different cell types. Thus not less than four distinct types of islet cells have been characterized each of them being the source of a biologically active and chemically well-defined polypeptide. Since some of the cell types and their associated secretory products have been described only within the last few years it may be relevant to review here our current status of knowledge in this field The description will be confined to the mammalian islet organ with special attention to the human islets

The predominant islet cell type is the *B-cell* which makes up about 60 per cent of the human endocrine pancreas This cell was described already at the beginning of this century and is by far the most well defined of all the islet cell types. Its role as the source of insulin was recognized over four decades ago and today the knowledge of the mechanisms of insulin formation and release has expanded to include even the most detailed molecular events (see below) From a structural point of view the B-cell is easily identified in the light-microscope with the aid of immunocytochemical techniques or with conventional histological staining reactions such as chrome alum hematoxyline or aldehyde-fuchsin (Fig. 1) An ultrastructural picture of the B-cell is given in Fig. 2

Among other islet cells the A_2*-cell* (or A cell) is the most well defined This cell is the source of pancreatic glucagon, a hormone which has recently been suggested as contributing to the development of human diabetes (21) The human A_2-cell is stained distinctly with Grimelius silver impregnation technique and in some species there is also a positive tinctorial reaction for try

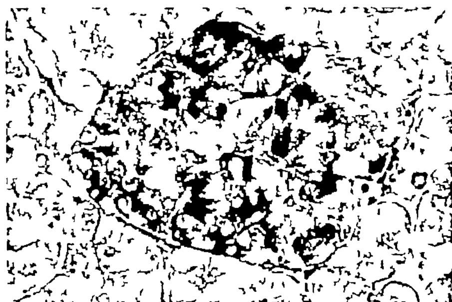


Fig 1 A Bouin-fixed section of human pancreas stained with aldehydfuchsin trichrome. Dark B-cells are scattered all over the islets. ×400.

reflecting the presence of this amino acid in the glucagon molecule. In the human islets these cells are typically located in the periphery and also along the islet capillaries (Fig. 3) Altogether the A_2-cells make up about 25 per cent of the human endocrine pancreas.

The *A_1-cell* (or D-cell) is the cell of origin of somatostatin or a compound with somato- -like immunoreactivity (10 18) While A_1-cell usually comprises less than ten per cent of the islets of laboratory animals they seem to be relatively more common in the human islets In the light microscope the cells are characterized by a positive reaction with the Hellerström-Hellman silver impregnation procedure (Fig 4) Although the precise physiological role of pancreatic somatostatin is so far obscure it is of considerable interest that this compound is a powerful inhibitor of both insulin and glucagon secretion. This observation together with the reported improvement of glucose homeostasis in juvenile diabetes during somatostatin infusion (9) suggests a possible glucoregulative function of somatostatin. Indeed there are several reports indicating a relationship between the pancreatic somatostatin content and diabetes mellitus Thus in juvenile diabetes hyperplastic changes of the A_1-cells have been observed (17) Also both cases of somatostatin producing tumours which have been reported thus far were accompanied either by diabetes or a diabetic glucose tolerance test (6 11)

The fourth and most recently discovered of the islet cell types has been named the *PP cell* (12) As the (tentative) name implies this cell is the source of pancreatic polypeptide a protein composed of 36 amino acid residues in a straight chain. In the human islets the PP cells are relatively rare but they occur also in the acinar parenchyma (12) They exhibit negative staining reactions to both aldehyde fuchsin and the silver techniques but have a relatively characteristic ultrastructural appearance Their biological significance is so far obscure but the fact that they seem to exhibit a marked proliferation in juvenile diabetes (see below) makes them a quite interesting object of clinical studies

THE NORMAL B-CELL

There are few cells in the human body which are functionally better characterized than the B-cells. Not only has a great attention been paid to the mechanism of insulin release but there has also been accumulated a detailed knowledge of the various steps in the forma-



Fig. 2 Electron microscopic view of mouse B-cell in collagenase isolated islet of Langerhans. The nucleus with its chromatin is surrounded by a nuclear envelope with pores. The most prominent features of the cytoplasm are the numerous secretory granules with wide membranous sacs. Occasionally the dense core of granule is needle-formed. Throughout the cytoplasm there is rough endoplasmic reticulum mainly of the vacuolar form. The Golgi-apparatus to the left of the nucleus is well developed. Mitochondria comprise 4–6 per cent of the cellular volume. They are round or elongated and have dense matrix and an orthodox arrangement of the cristae ×8 700. (Electron micrograph by the courtesy of Dr L. A. H. Borg, Uppsala.)

tion of the insulin molecule. Altogether these two phases of B-cell function comprise an exceedingly complicated cellular machinery which theoretically provides countless possibilities for damage. As we will see below there are nevertheless several fairly well defined working hypotheses as to how such injury is caused by various diabetogenic factors.

The insulin formation is initiated by a coding process governed by the genetic material of the B-cell nucleus. Recent progress in molecular biology and the isolation of the messenger RNA for insulin (⁹) has made possible the identification and cloning of the insulin gene itself (20). It is indeed very likely that the full and detailed structure of this gene will be elucidated in the near future. As a result of studies in this field it is now clear that the formation of the insulin molecule occurs in three steps the first of which is the synthesis of a very short-lived polypeptide called preproinsulin. Within seconds or minutes after its formation this peptide is cleaved into one smaller fragment, possibly serving as a binding factor between the ribosomes and the membranes of the endoplasmic reticulum and a larger and more complicated molecule which comprise the well-known proinsulin. This

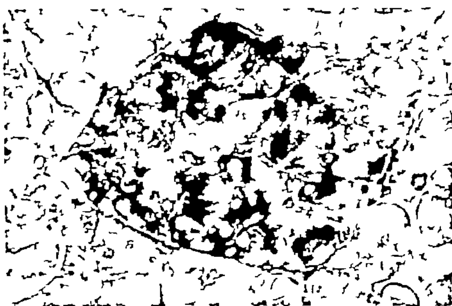


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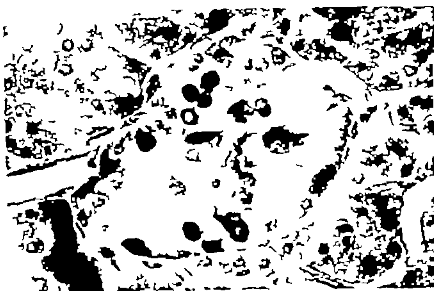


Fig 4 Section of human pancreas fixed in Bouin's *solution and stained with* Hellerström–Hellman's argyrophil technique. The dark A_1-cells (D-cells) are polymorphic and sometimes markedly elongated. ×500.

THE DIABETIC B-CELL

The central role of the B-cell in the etiology of diabetes has been recognized for a long time and it is well established that diabetes is a disease of complete or partial insulin lack. It is of great interest in this context that a diminution of the B-cell mass has actually been found both in juvenile and in maturity onset diabetes. Thus Gepts in his now classical studies on chronic juvenile diabetes (7) demonstrated an almost complete disappearance of the B-cells with most of the remaining islets being composed of glucagon- and somatostatin-producing cells. Surprisingly some islets consisted of a high proportion of cells with a positive reaction for pancreatic polypeptide and were regarded as reflecting a kind of atypical islet cell regeneration (8). In maturity onset diabetes the B-cell mass appears to be less affected but may nevertheless be diminished by 50 per cent or more (22). Although a diminution of this magnitude may not be sufficient to cause diabetes in otherwise normal individuals it may well be of critical significance when insulin resistance is part of the etiology.

Let us now take a look at some possible diabetogenic mechanisms which may primarily affect the B-cell. There are now multiple lines of evidence to indicate that both the patient's genetic predisposition and the environment to which he is exposed are of significance in this context (3). However the way in which these factors are linked together seems to be quite different in juvenile and maturity onset diabetes. In the insulin dependent juvenile group there is an increased incidence of certain histocompatibility types or HLA antigens (HLA-B8 HLA BW15 or both) (16) but the inheritance of the disease as such seems fairly low. On the other hand studies of identical twins of whom at least one had diabetes, showed that there was a high tendency for the non-diabetic to develop diabetes when this was of the maturity onset type (19).

It is furthermore worthy of note that in insulin-dependent diabetics both cell-mediated autoimmune reactions towards the islets ("insulitis") (13) humoral islet cell antibodies (14) and an increased incidence of certain viral antibodies (4) have been demonstrated. A seasonal variation in the onset of juvenile diabetes (5) suggests that autoimmune reactions could be combined with a seasonal factor for example of viral origin.

Thus, we end up with a set of clinical observations which may explain at least in part

tial centrifugations, and the raise of specific anti-hagfish-insulin antibodies, will be given in separate monograph (Emdin, in preparation)

INVERTEBRATES

As early as in 1923 it was claimed that insulin might be produced not only by higher vertebrates but also by invertebrates (9) It was however not until some 13 years ago that the first invertebrate insulin viz. starfish insulin was isolated and characterized biologically and immunologically (31) Later on several more insulins from both protostomian and deuterostomian invertebrates were discovered (cf 9 10) but so far no invertebrate insulin has been purified to homogeneity and further analysed with respect to its primary structure biosynthesis and three-dimensional molecular structure

When the cellular sites of the production of insulin in invertebrates were sought, it became clear that the B-cells in the islets of Langerhans of higher vertebrates could have been derived from the mucosa of the alimentary tract (possibly with a neural crest origin) (cf 9) In both protostomian (16) and deuterostomian (29) invertebrate species it could be shown by light microscopy immunocytochemistry and transmission electron microscopy that the insulin-containing cells were of open type in some species there were even signs of extrusion of secretion granules into the lumen of the gut allegedly as a response to stimulation to insulin secretion (cf 9)

This structural evidence that the invertebrate insulin-producing B-cells can be exocrine—like once the original thyroid follicular cells (cf 1?)—has given some new morphological support to a 10-year-old working hypothesis on the evolution of insulin (8 24 25 26) According to this one of the digestive enzymes secreted from the mucosa of the alimentary tract during the period of digestion and resorption of food was a proinsulin-like protein i e a "protoproinsulin" As digestion proceeded this proinsulin-like protein itself may have undergone cleavage by proteolytic enzymes and an insulin-like protein became unmasked and resorbed into the blood stream and/or in other body fluids When digestion was completed the secretion of this protoproinsulin ceased and the insulin-like protein disappeared from the blood and/or other body fluids

Some new biochemical aspects of this hypothesis can be said to have been obtained by the recent discovery or preproinsulin (3) It is now of great interest to analyse biochemically the secretory product of the gut-connected B-cells of protostomian and deuterostomian invertebrates in order to see whether preproinsulin and/or still larger precursor stages of the hormone can be found.

VERTEBRATES

As shown in preceding reviews from our laboratory (9 10 15) a clue to insulin evolution may be found in the islet parenchyma of the cyclostomes The two extant representatives of this diphyletic group the hagfishes and the lampreys are descendants of the Ostracoderms that lived about 350–400 million years ago and are supposed to be close to the earliest vertebrates (14 20) Here for the first time in evolution a separate islet organ is formed occurring even before the development of an exocrine pancreas This cyclostomian islet parenchyma contains only insulin-producing B-cells and somatostatin-storing D-cells whereas the glucagon-immunoreactive A-cells still remain in the gut mucosa as endocrine cells of open type (20) That the cyclostomian islet parenchyma actually forms a link between the gut-associated B-cells of the invertebrates and the islets of Langerhans in higher vertebrates is shown by the recent observation that even in adult lampreys some remnants of B-cells of closed type can be found in the mucosa of the anterior parts of its primitive intestinal tube (15) In the hagfish all the B-cells have left the gut mucosa but some

remain in the bile duct mucosa which is the origin of the hagfish islet parenchyma (20)

Hagfish insulin

Amino acid sequence crystalline structure receptor binding affinity and biological activity The amino-acid sequence of hagfish insulin has been reported (13 22) the insulin has been crystallized (21) and its three-dimensional structure has been studied by X-ray crystallography (4) recently refined to 3 1 Å (5) In brief the regions in the insulin molecule that are known to be species invariant are with one exception, all preserved in hagfish insulin s primary structure The three-dimensional pattern of the hagfish insulin dimer is almost superimposable on the pig insulin dimer Apart from some minor differences there is only one obvious alteration, viz. that the C terminal end of the B-chain is folded back over the N terminal end of the A-chain. Some biological properties of hagfish insulin in isolated rat fat cells have been described (7) Here, a unique feature of hagfish insulin was demonstrated its binding affinity was 23% and its potency only 5% of that of pig insulin. Hagfish insulin might therefore be characterized as a "partial antagonist" on the receptors. It could also be shown, that this discrepancy between binding and potency was not due to the presence of the extra-B_{31} methionine residue, present in hagfish insulin. Thus its "antagonistic" property still remains an enigma.

Biosynthesis A decade has now elapsed since the discovery of proinsulin (24) In that interval similar mechanisms have been found to operate in the formation of several peptide hormones and also for certain viral capsule proteins collagen and serum albumin (27) These all have in common the formation of a precursor and its subsequent conversion due to limited proteolysis. The mechanism of synthesis of insulin via proinsulin has been identified in all species investigated so far including some teleost fish (25 26) of insulin biosynthesis in *Myxine* re-



Fig 1 The effect of temperature on conversion of hagfish proinsulin to insulin. Batches of 5 hagfish islet organs were pulsed for 30 hours in the presence of ³H-leucine at 11°C, and then chased for another 12 hours at the temperatures indicated below Afterwards, the islet organs were extracted with acid ethanol and fractionated over Bio-Gel P 30 columns (100 1 cm) eluted with 3 M acetic acid, and the radioactivity was measured. *Top* Elution profiles of extracted islet organs after 12 hours chasing at 2°C (dots), 13.5°C (solid triangles) and 31.5°C (open triangles). PI = proinsulin; I = insulin. *Bottom* Rate of conversion, calculated as indicated in Table 1 plotted vs. temperature.

ported (26) As a whole *in vitro* biosynthesis proceeds slowly in the hagfish at low temperatures. For instance the half time of conversion at 11°C is 10 hours, whereas that at 18°C is around 8 hours. The temperature dependence of the converting enzyme system operating in the hagfish is shown in Fig. 1 A maximum rate is obtained above 20°C. Fig. 1 also shows that there is no evidence for multiple ing systems, with different K_m op



Fig 2 The effect of temperature on total proinsulin and insulin synthesis. Batches of 5 hagfish islet organs were incubated for 48 hours at different temperatures in the presence of ^{3}H-leucine. The sum of the radioactivities in the proinsulin and insulin peaks in each experiment was assessed and plotted against the incubation temperature. Otherwise extractions and calculations were performed as indicated in Fig. 1

in different temperature intervals as may be seen in other enzyme systems in poikilothermic vertebrates (17)

The temperature dependence of the rate of proinsulin synthesis in the hagfish has also been studied Fig. 2 shows that the maximum rate of the proinsulin-insulin biosynthesis occurs at around 20°C whereas the biosynthesis ceases at 30°C

The temperature of the natural habitat of the hagfish in usually about 5°C and can be assumed to seldom exceed 10°C (12 20) Since both the rate of conversion and the rate of proinsulin synthesis are temperature-dependent it is noteworthy that the rate of increase of conversion is greater than the corresponding increase in the rate of proinsulin synthesis for a given temperature elevation

In order to find the time needed for the hagfish B-cells to process proinsulin on the ribosomes to convert it and finally to secrete it experiments were performed in which hagfish islet organs were incubated for 20 hours at 11°C with ^{3}H-leucine and then pulse-chased (26) The medium was replaced at given intervals and its radioactive insulin content determined. The results are shown in Fig. 3 There is a lag-phase of 20 hours before the newly converted insulin has passed through the B-cell and is released After 60 hours only about 5% of the total insulin synthesized has been secreted. For a presumed (pro)insulinotropic agent it will then take 40 hours before its message to increase the quantity of proinsulin synthesized is processed into extra-cellular insulin. It may then be considered reasonable that for an acute need of insulin the hagfish must rely upon stored hormone reserves Preceding experimental studies from our laboratory (cf 12) have shown that one of the most conspicuous features of the blood sugar regulation of the hagfish is the sluggishness of all its reac

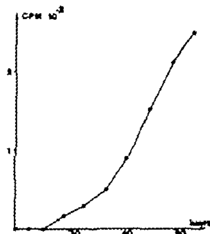


Fig 3 Time-course of secretion of *de novo* synthesized proinsulin-insulin. Twenty-five islet organs were pulsed for 20 hours at 11°C. This is a time interval corresponding to the time period needed by the islet organs to synthesize sufficient amounts of labeled proinsulin, but not to convert it. The islet organs were then chased for the time periods indicated and the chasing medium was replaced with new chasing medium at given intervals. The labeled insulin was then measured and the accumulated amount of *de novo* synthesized insulin was plotted against time. No significant amounts of labeled proinsulin could be detected. The "0-time" indicate the beginning of the chase period. Otherwise, extractions and calculations as in Fig 1





Fig. 4. Transmission electron micrographs of hagfish islet β-granules. *Left:* Ultrastructural appearance of Fraction 2, pellet, as specified in Table 2. The β-granules can be clearly seen, mostly with intact limiting membranes. In addition, some material which is hard to identify occurs. *Right:* For comparison, a picture of the fine structure of the β-granules from intact islet organs are included. Preparations as given in the preceding report from our laboratory (20). 52000.

tions to various procedures supposed to affect the blood glucose level.

Glucose is a positive modulator of proinsulin biosynthesis in higher vertebrates (25). It does not, however, convincingly alter the rate of conversion (25). This also holds true for the proinsulin-insulin biosynthesis of the hagfish. As can be seen from Table 1, addition of glucose to the incubation medium neither stimulates proinsulin biosynthesis nor does it affect the rate of conversion. Similar results were obtained in analogous experiments with a number of other substances, such as 2.3 mM arginine, 3.0 mM leucine, 1.0 mM 3-isobutyl-1-methyl-xanthine (IBMX), 10 mM theophylline, and 10 mM di-butyryl cyclic adenosine-mono-

Table 1. *Effects of D-glucose on incorporation of ³H-leucine into proinsulin and insulin and the rate of conversion*

CPM = counts per minute

D-glucose (mM)	Conversion (%)	Incorporation (CPM × 10^{-3})
0	60.8	26.8
0.6	50.2	20.2
1.7	57.2	30.1
5.6	56.5	22.1
16.7	50.5	22.4
27.8	50.9	23.6

Batches of 5 islets were incubated with ³H-leucine at 18°C for 48 hours. After acid-ethanol extraction and gel-filtration the amounts of labeled proinsulin and insulin were calculated. Conversion (%) was calculated as:

$$100 \times \frac{\text{Insulin CPM}}{\text{Proinsulin CPM} + \text{Insulin CPM}}$$

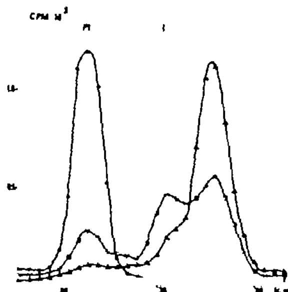


Fig 5 Tryptic digestion of labeled hagfish proinsulin. Endogenously ^{3}H-leucine-labeled proinsulin was incubated with 0.1 μg of trypsin in a Tris-HCl-buffer pH 8.0 with 2 mM $CaCl_2$ at 25°C. The digest was then gelfiltered, as indicated in Fig. 1 *Dots*. No trypsin, *Circles* 5 minutes incubation, *Triangles* 10 minutes' incubation.

phosphate (cAMP) In view of these data we feel tempted to speculate that the hagfish may lack a positive modulation of proinsulin biosynthesis. Perhaps it possesses some sort of a negative feed-back system. It may also be that the rate of synthesis is constant for a given temperature and that the mature granules that are not secreted disintegrate and their insulin content is degraded within or outside the B-cell. Some structural aspects on the latter speculation can be given by the occurrence of cavities of degenerative nature within some islet lobules (11 12) the presence of lysosomal dense bodies (2) and the peculiar "connective tissue secretion" of membrane-release pattern to foliate processes of the basal membrane (20)

Conversion and fine structure of the β-granules The cores of the β granules of pancreatic islet B-cells of several vertebrates are often crystalline (19) It is believed that this intragranular crystallization may serve to protect the newly converted insulin from further digestion (1) *In vitro* the B_{22} arginine residue is susceptible to tryptic digestion, but hexamerization with crystallization is said to protect this peptide bond (1) Moreover further protection is offered by the fact that in most insulins the B_{21} residue has a free carboxyl group known to reduce the rate of hydrolysis of a juxta-positioned basic residue

Although *Myxine* insulin readily crystallizes *in vitro* there is no morphological support for crystalloid structures within the *Myxine* β-granules (20) (Fig. 4) The only crystalloid structures regularly found in hagfish islet parenchymal cells are crystalline inclusions probably or proteinaceous nature localized to the granular endoplasmic reticulum and occasionally also closely associated with annulate lamellae (2) However these crystalloid structures occurred mainly in the cells with spherical secretion granules now known to produce somatostatin (9 30) and in agranular cells (probably of precursor nature) If the idea that intragranular crystallization serves to protect sensitive insulins is correct, why is it then that *Myxine* has not adopted this mechanism, since the presence of a B_{22} arginine residue and a B_{21} valine uncharged residue in *Myxine* insulin makes such a protection highly desirable?

We have observed that endogenously ^{3}H labeled *Myxine* proinsulin and insulin are both

Table 2 *Distribution of immunoreactive insulin (IRI) in hagfish islets fractioned by differential centrifugation*

	Fraction	IRI % of total
1	900 g × 10 min pellet	<2
2	15 000 g × 15 min pellet	77
3	100 000 g × 60 min pellet	8
4	100 000 g × 60 min supernatant	14

Twenty-five islets were homogenized in phosphate-buffered sucrose (0.25 M) with electrolytes and bovine serum albumin at pH 6.0 and centrifuged as indicated above. The pellets and supernatants were assayed radioimmunologically for their total hagfish insulin content with a specific anti-hagfish-insulin antibody

Fraction number 1 contains mainly nuclei, Fraction number 2 consists mainly of secretion granules (Fig. 4 B)' Fraction number 3 is the microsomal fraction, containing the endoplasmic reticulum.

extremely sensitive to tryptic attack. Thus in accordance with the structural arrangements in hagfish insulin trypsin rapidly splits off a nonapeptide from the C-terminal part of the B-chain giving rise to des-nonapeptide-insulin. In the case of labeled hagfish proinsulin the mildest tryptic conditions that produce any hydrolysis yield a protein co-eluting with hagfish insulin but also in roughly equimolar amounts, a protein that appears to be des-nonapeptide-insulin Thus we have, so far failed to find a specific condition, utilizing trypsin in which proinsulin is converted to intact insulin rather than to a degraded hormone. The results of such an experiment are shown in Fig. 5

It has been shown that conversion—at least partially—occurs within the β-granules in higher animals (25) Could it be that conversion in the hagfish is completed before the protein has reached the granules? By differential centrifugation after incubation with ³H-leucine it was found that under certain conditions the ratio of labeled proinsulin/insulin was ten-fold higher in the granule fraction (Fig. 4B) than in the normal total islet parenchyma. The results of these experiments are shown in Tables 2 and 3 These data suggest that at least part of the conversion must take place within the β-

Table 3 *Biosynthesis and conversion in incubated and fractionated hagfish islets*

PI = proinsulin n.d. = not detected

Hours of incubation		$100 \cdot \frac{{}^3\text{H-proinsulin CPM}}{{}^3\text{H-proinsulin CPM} + {}^3\text{H-insulin CPM}}$			
		Fraction			Acid ethanol extracted islets
Pulse	Chase	1	2	3	
48	0	d.	d.	PI only	PI only
48	24	n.d.	43.1	n.d.	44 0
48	48	n.d.	15.6	d.	15 9

Batches of 25 islets were incubated (pulse-chase experiments) with ³H-leucine as indicated. Twenty islets were homogenized and fractionated as described in Table 2. The fractions were then extracted with acid ethanol and gel-filtered The remaining 5 islets were extracted with acid ethanol and gel-filtered without prior fractionation. Radioactivity was counted and the ratio indicated abov was calculated.

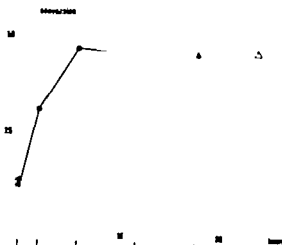


Fig 6 Blocking of proinsulin conversion with antimycin A. Batches of 5 islet organs were pulsed in the presence of ³H-leucine for 6 hours at 11°C, followed by chase period at the same temperature for 4 hours. Antimycin A was added at different times during the chase. Extraction and fractionation was carried out as in Fig. 1 The rate of conversion was calculated as in Table 1 Arrows indicate the times when the antimycin A was added. The percent conversion in a pulse control experiment is indicated by solid triangle. The percent conversion in an antimycin-A-free control after 24 hours' chase is indicated by an open triangle.

granules otherwise one would find a much higher total content of proinsulin in hagfish islets.

Further support for this similarity between the insulin biosynthesis of *Myxine glutinosa* and that of higher vertebrates is given by the fact that conversion of the newly synthesized proinsulin does not begin until it has been transported to the Golgi apparatus or its vicinity This can be shown by pulse-chasing islets in the presence of antimycin A a potent inhibitor of oxidative metabolism and consequently also of the energy-dependent transport from the ribosomes to the Golgi complex (cf 25) If antimycin A is added at various intervals during a chase after a brief labeling period with ³H leucine conversion can only be blocked when the proinsulin is in transit and before it has been engulfed by the Golgi complex and/or the granules where antimycin has no effect. Similar experiments have previously been performed on rat islets (cf

The results of such a set of experim

Myxine islet B-cells are shown in Fig 6 They show that if added early enough, antimycin blocks conversion, since the transport of pro-insulin is stopped The time of transit is approximately 3–5 hours

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Insulin from other lower vertebrates

In current studies on the molecular structure of insulins from other lower vertebrates we have so far collected material and made crude insulin extracts of the islet parenchyma from three species One is a representative of the other extant cyclostomes viz the *Petromyzontia* (12) Here we have chosen the river lamprey *Lampetra fluviatilis* The cyclostomes or *Agnatha* can be said to form a sister group to all the other vertebrates viz. those equipped with jaws the *Gnathostomi* (9 11 14) Among the most primitive of the gnathostomian vertebrates we have chosen a representative of the cartilaginous fish (*Chondrichthyes*) viz the spiny dogfish *Squalus achantias* and a bony fish (*Osteichthyes*) viz. the daddy sculpin, *Cottus scorpius* So far we have only some compositional data to offer

An analysis of the simple amino-acid compositions of insulins from the river lamprey and the spiny dogfish shows that the numbers of individual amino-acids are large enough to account for all the invariant positions and—with two exceptions in lamprey insulin and one in dogfish—all the so-called conservative positions as well (13) The number of amino-acid substitutions between lamprey and hagfish insulins is 9 whereas that between dogfish and hagfish insulins is 21 Hagfish insulin differs from pig insulin in 23 positions of which only 12 can be considered to be "radical" substitutions (13) The corresponding figures for lamprey and dogfish insulins are 16 and 12, respectively (13) So far we have no analogous data to offer for sculpin insulin.

From our observations on the molecular structure of hagfish insulin (see above) it seems justified to assume that also in lamprey and dogfish insulins the variations observed are restricted to positions already now known to be highly variable If so these evolutionary studies of insulin will confirm the results of analogous investigations in other proteins viz. that relatively small variations are observed in the length and basic structure of polypeptide chains whereas substitutions in certain amino-acid residues are common (13)

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(*S. F.*) Department of Pathology
University of Umeå
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be supposed that any mutations have been unsuccessful. Do you think we can conclude from this that there are almost no chances to find a more elementary polypeptide with preserved biological activity?

Sture Falkmer Our phylogenetic observations all indicate that it is only the kind of insulin molecule whose basic features are found in the hagfish and in the pig insulin that has insulin s fundamental biological effects

STRUCTURAL ANALYSIS OF THE MOLECULAR EVOLUTION OF SOME GASTRO-ENTERO-PANCREATIC HORMONES

HERBERT GOTTFRIED GREGG MAMIKUNIAN STURE FALKMER, STEFAN O EMDIN
ELLIOT LANDAW[a] and BERGE DADOURIAN[a]

From the Department of Molecular and Theoretical Endocrinology Inter Science Institute Los Angeles Department of Pathology University of Umeå Umeå, Sweden, and [a]Department of Biomathematics School of Medicine University of California at Los Angeles California, USA

ABSTRACT By means of a statistical analysis of the occurrence of amino-acid residues in the polypeptide chains of several gastro-entero-pancreatic (GEP) hormones an investigation was undertaken to determine whether any of these hormones might be related to each other—possibly from an evolutionary point of view Particular interest was paid to the occurrence of small charged segments, i.e. those with acidic or basic amino acid residues, since such segments can be presumed to play a role in hormonal receptor binding mechanisms. By this method hormonal relationships were suggested by the observation that these small charged amino-acid sequences, contained in the hormonal structures, match as a result of non-randomness. It was found that hagfish and human insulin were related on a molecular level not only to the newly discovered (avian, bovine, human) pancreatic polypeptide (PP) but also to some other GEP hormones (VIP GIP glucagon) as well as to calcitonin and to the α-subunit of the glycoprotein hormones. Interpretation of the statistical data suggests that all these peptide hormones are related by a common hexapeptide sequence which contributed, at an evolutionary point, to their molecular architecture. A hexapeptide segment of APP is statistically related to sequences of equal size in the carboxy terminal region of the A-chain of both hagfish and human insulin, providing the first instance of their structural similarity Correlations between PP insulin, glucagon, VIP and calcitonin provide a tentative basis for predicting the production of one or more of these peptide hormones by immature or de-differentiated cells of neoplasms and non-neoplastic pathologic lesions of the GEP endocrine system.

The possibility that a close interrelationship exists between polypeptide-producing nerve cells and cells of disseminated or compact endocrine organs was already suggested in the 1920s (10) During the last decade renewed interest was raised by the discovery of several structural and functional features that all these neurosecretory and endocrine cells have in common (22) In particular the amine precursor uptake and decarboxylating (APUD) properties of cells of these kinds in various locations contributed to the creation of concepts such as the "APUD family" "Paraneurons" (endocrine cells of neuronic nature and nerve cells with endocrine characteristics) and to some extent also the "gastro-entero-pancreatic" (GEP) endocrine system (10 22) Evidence in favour of a common origin of all these cells from the neural crest and/or the neural tube and ridge has been presented (22) As a matter

Visiting Research Associate, Department of Pathology University of Umeå, Umeå, Sweden, on leave from the Department of Molecular and Theoretical Endocrinology Inter Science Institute Los Angeles. Dr Gottfried died on October 15 1977

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of fact, the whole field of peptide endocrinol ogy now seems to have become neuroendocrinology (cf 22) These concepts have offered a new approach to solving some crucial problems in the pathology of endocrine neoplasms in general, for instance multiple endocrine adenomas (MEA) and of islet cell tumors in particular (cf 7)

In addition to this approach to elucidate endocrine problems in multiple-hormone-producing tumors and pathologic states with "aberrant" hormone production in the GEP endocrine system, there are also several investigations in which production of the different GEP polypeptide hormones and their precursors has been detected by immunological and chemical techniques (cf 5 7 25) By applying theoretical analytical methods to the amino-acid sequences of these polypeptide hor mones plausible "evolutionary trees" of the GEP hormones have been made, forming a speculative explanation to the observations that "aberrant" polypeptide hormones can appear in diseases of various kinds in the GEP endocrine system (7 22 32, 34)

Some of us (H G G M E. L. & B D) have further elaborated the latter kind of analysis of hormone interrelationships by apply ing statistical methods to charged segments of polypeptide chains i.e. amino-acid se quences of 5–10 residues, containing one or more of either acidic amino-acid residues (Asp Glu[1]) or basic ones (Arg, Lys) which are of particular interest in seeking homologies between various polypeptide hormones (12) The reason for this is that such charged se quences can be presumed to play a role in the interaction between hormone receptors of target cells and binding sites of the hormone molecules. Then, by calculating the probability that such small charged amino-acid segments of the same or similar kinds occur more often than by mere chance in some polypeptides it seems reasonable to suggest that such peptides with charged sequences in common may be related from an evolutionary point of view (4 6 12 13 19) If a molecular interrelationship is suggested from such a statistical analysis it may be possible to explain why onto- or phylogenetically or neoplastically immature or de-differentiated GEP endocrine cells can deviate in their hormone production to manufacture these related polypeptides instead of—or in addition to—the normal hor mone (cf. 7 12 13)

With regard to the aims of this symposium we thought it might be of some interest to evaluate by statistical analysis of the molecular structure of insulin whether it might have some relationship to the newly discovered pancreatic polypeptide (PP) (15 18) Increased concentrations of PP in the blood and endocrine pancreas are known to occur in diabetes mellitus of juvenile type in persistent neonatal hypoglycemia with hyperinsulinism, and in several kinds of islet-cell neoplasms (cf 7 9 22, 24) Detailed information of the molecular structure of insulin is available from the most primitive vertebrate (hagfish) as well as many highly developed vertebrate species (8) An analysis of whether any homology exists between these two hormones (insulin and PP) may also add an extra dimension to our under standing of how these pancreatic islet poly peptides were assembled during vertebrate evolution. In a concomitant report by some of us (H G E. L. B D & G M) it has already been shown that an analysis of charged segments of PP (avian and bovine) indicated a relationship of PP to the recently discovered vasoactive intestinal polypeptide (VIP) as well as to calcitonin (12) Therefore these hor mones and some other GEP hormones were also included in our analysis

METHODS

Mathematical methods and discussion

Raw probability scores between given amino acid sequences were calculated by the McLachlan "double matching matrix method" (6, 13 19). This method ... symmetric 20×20 score matrix based on the

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[1] The abbreviations of the amino-acid residues made in this report are those used conventionally (4).

point amino acid substitution frequencies empirically derived from 16 families of known homologous proteins (19).

For any pair of amino acids a score ranging from 0 to 9 is given, a higher score indicating a more frequent substitution, perfect scores of 8 or 9 being identity between two amino acids. Identities involving Cys, Phe, Tyr and Trp receive scores of 9. For a given pair of amino acid sequences, each of span length *S* a total score (*M* value) is derived by summing the *S* individual pair scores. The probability for a particular *M* value for a span length *S* is defined as the chance of observing such a score or greater by chance alone after drawing with replacement *S* pairs of amino acids at random (one member of a pair from protein A, and the other from protein B). These calculations require only a knowledge of the fractional amino acid compositions (F_i and F_j) of proteins A and B. In addition, as suggested by Greller and Erhan (13) the probabilities were also calculated using the Dayhoff set of frequencies of the "Universal Protein" instead of F_j (the fractional composition of the B protein itself) (4). These two calculated probabilities (denoted *P* (F_j) and *P* (F_j^*) in Table 1 are the probabilities calculated using the F_j of the B protein itself and F_j^* of the "Universal Protein" respectively gave essentially similar results, the probabilities reduced at most by a factor of 1/2 in only few cases when using the Dayhoff frequencies.

Determining the significance of these probabilities is a less precise matter. If *P* is the *M* score (*M* value) probability of a span length *S* of matching sequences of such span length, then the overall probability of observing such a score or greater is $1-(1-p)^n \approx np$ if $np \ll 1$. McLachlan (19) gives an upper level for $n = n_a \times n_b$ where n_a and n_b are the number of amino acids in proteins A and B. Thus, with two proteins of length 10^2 McLachlan requires a raw probability of about 10^{-6} for significance (specifically that the probability the given *M*-score could have occurred by chance alone being no more than 0.01). This estimate of *n* may be too large because neighboring overlapping sequence spans are *not* independent; in particular the estimate will be one or two orders of magnitude too large when only small "target" subsequences of the proteins are used for developing scores.

Greller and Erhan (6, 13) allow larger raw probabilities of 10^{-4} because they are interested in spans which have more than one perfect match, and they estimate this to reduce the number of independent matches by about two orders of magnitude. A difficulty in this estimate is that spans having multiple perfect matches also tend to be those with higher *M*-scores.

In this paper we are interested in spans which are charged and this reduces the number of independent matches by 1–2 orders of magnitude. The charged amino acids (Lys, Arg, Asp, Glu) represent only 1/5 of the total. Assuming that all amino acids are equally likely one can estimate the proportion of all possible sequence pairs of length 6 (our average span length) with 2 or more charged amino acids per span to be 1 $\times 10^{-}$ and those with 3 or more charged amino acids to be 9.8×10^{-2}. Since spans with high proportions of charged amino acids would also tend to have higher *M*-score than average by chance alone we attempted to estimate this effect.

For a span length of 6, using the Dayhoff frequencies, an *M*-score of 38 gives a raw probability of 1.2×10^{-4}. For a protein which is 50 % charged (i.e. 50 % of the amino acids being Lys, Arg, Asp Glu, and hence, on the average, any span length being 50 % charged) the raw probability for a span of 6 with *M*-score 38 increases only to 3.6×10^{-4}. Similar estimates for *M*-scores of highly charged spans show the probabilities increase only by a factor of 2 to 3.

In summary these crude estimates show that when looking specifically at charged spans, the average *M* score of such spans is increased by a factor of 2 to 3 while the proportion of candidate spans is 10^{-1} to 10^{-2} of the total. This yields a decrease in the raw probability on the order of 3×10^{-1} to 2×10^{-2}, namely a raw probability (when matching charged spans) of 10^{-3} is approximately equivalent in significance to a raw probability of 10^{-4}.

Methods used for tracing small charged peptide sequences which relate peptide hormones to each other and to other proteins

Apparent homologies in charged sequences between two proteins, ranging in size from 5–10 amino acids were evaluated statistically by the double matching matrix technique. When a statistically related match was found between two proteins, the A protein (primary span) and the B protein (target span) then the primary span was used to find similar target sequences in a second protein.

When apparent homology was found between a primary span and the target span of a second protein, the double matching probability of that match was calculated. The process was repeated with either the original primary span or the new target span (as the primary span) for searching a new (third) protein sequence for homologies.

Source proteins

The amino acid sequences compared by the double matching matrix statistical computations were obtained from the known protein structures (4):

(*a*) *GEP Hormones.* Hagfish insulin (23) human insulin, avian, bovine, and human PP (APP BPP and HPP respectively) VIP gastric inhibitory peptide (GIP) and pro-glucagon (31)

(*b*) *Thyroid hormones* Human and bovine calcitonin, salmon calcitonin I, II and III.

(*c*) *Other polypeptides* The glycoprotein α-subunit 39–48, the subunit of the intact α-β complex of thyrotropin (TSH), luteotropin (LH) and follicle-stimulating hormone (FSH).

Results of double matching probabilities

The double matching *P* values express the chance that the match between the sequence of the A protein and the B protein occur as a result of randomness (Table 1).

The statistical results of matching small charged sequences contained in one peptide hormone with that present in another is referred to as the match between the primary and target sequences, respectively. In Table 1 the double matching probabilities are given for each sequence match of the A protein (primary sequence) against the B protein (target sequence). The fifth column

Table 1 *Statistical data relating the peptide sequences shown*

The *M* value is the total McLachlan score for each peptide sequence compared. The *P* (*Fl*) indicates the probability value obtained for the matched sequence using the fractional composition of the B protein (see Methods) itself, while the *P* (*Fξ*) indicates the probability values obtained for the same sequence match using the Dayhoff Universal Protein (see Methods) for the fractional composition of the B protein. The *P* values in both cases are the double matching matrix computation.

Sequence number	Peptide sequence		*M* value	*P* (*Fl*)	*P* (*Fξ*)
1	VIP 21–26 Bovine Calcitonin 14–19	Lys Tyr Leu Asn Ser Ile Lys Asp Leu Asn Asn Tyr	33	1.9×10^{-6}	2.03×10^{-6}
2	VIP 21–25 Glucagon 12–16	Lys Tyr Leu Asn Ser Lys Tyr Leu Asp Ser	38	5.09×10^{-6}	2.45×10^{-6}
3	VIP 21–26 Glucagon 12–17	Lys Tyr Leu Asn Ser Ile Lys Tyr Leu Asp Ser Arg	39	1.1×10^{-4}	5.58×10^{-6}
4	VIP 18–24 BPP 23–29	Ala Val Lys Lys Tyr Leu Asn Asp Leu Arg Arg Tyr Ile Asn	40	3.24×10^{-4}	4.09×10^{-4}
5	VIP 19–24 APP 24–29	Val Lys Lys Tyr Leu Asn Leu Gln Gln Tyr Leu Asn	38	1.25×10^{-4}	1.08×10^{-4}
6	VIP 12–16 GIP 16–20	Arg Leu Arg Lys Gln Lys Ile Arg Gln Gln	30	1.47×10^{-6}	1.13×10^{-6}
7	APP 15–20 Human Calcitonin 14–19	Gln Asp Leu Ile Arg Phe Gln Asp Phe Asn Lys Phe	33	1.25×10^{-6}	1.41×10^{-6}
8	APP 15–29 Salmon Calcitonin I, II, III 14–19	Gln Asp Leu Ile Arg Phe Gln Asp Leu His Lys Leu	33	(I) 1.42×10^{-6} (II) 1.53×10^{-6} (III) 1.29×10^{-6}	1.41×10^{-6} 1.41×10^{-6} 1.41×10^{-6}
9	APP 22–27 Human Calcitonin 14–19	Asp Asn Leu Gln Gln Tyr Gln Asp Phe Asn Lys Tyr	31	3.39×10^{-6}	3.92×10^{-6}
10	APP 23–27 Bovine Calcitonin 15–19	Asn Leu Gln Gln Tyr Asp Leu Asn Asn Tyr	30	8.66×10^{-4}	7.99×10^{-4}
11	APP 23–27 Human Insulin A-Chain 15–19	Asn Leu Gln Gln Tyr Gln Leu Glu Asn Tyr	30	8.46×10^{-4}	7.99×10^{-4}
12	APP 22–27 Human Insulin A-Chain 14–19	Asp Asn Leu Gln Gln Tyr Tyr Gln Leu Glu Asn Tyr	31	3.67×10^{-6}	3.92×10^{-6}
13	APP 22–27 Hagfish Insulin A-Chain 14–19	Asp Asn Leu Gln Gln Tyr Tyr Asn Leu Gln Gln Tyr	42	4.97×10^{-5}	3.94×10^{-6}
14	APP 14–19 HPP 21–26	Val Gln Asp Leu Ile Arg Ala Ala Asp Leu Arg Arg	32	5.04×10^{-5}	$2.37\times10^{-}$
15	APP 23–29 HPP 23–29	Asn Leu Gln Gln Tyr Leu Asn Asp Leu Arg Arg Tyr Ile Asn	45	5.01×10^{-6}	1.19×10^{-6}
16	VIP 12–21 Alpha Subunit 39–48	Arg Leu Arg Lys Gln Met Ala Val Lys Lys Arg Ser Lys Lys Thr Met Leu Val Gln Lys	56	$3.16\ 10^{-6}$	5.36×10^{-6}

In Table 1 (*P* (*Fl*)) gives the double matching probability of the A protein/B protein relationship when the fractional composition of the entire B protein (*Fl*) is used for the probability computation. The sixth column in Table 1 (*P* (*Fξ*)) gives the double matching probability of the A protein/B protein relationship using the Dayhoff Universal Protein (13) fractional composition values (*Fξ*) for the B protein in the statistical analyses. Two *P* values are, therefore, obtained for each comparison of an A protein sequence with B protein sequence.

In almost every instance, with the exception of a very few sequence matches, the double matching probability obtained using the Dayhoff Universal Protein fractional composition values for the B protein is slightly more

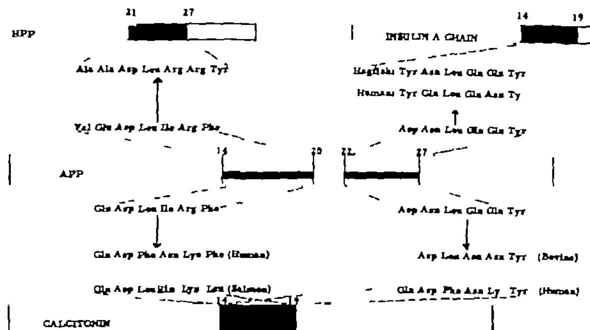


Fig 2 The relationship of charged sequences in APP to those in insulin, calcitonin, and HPP

interrelationship but it does support the concept that embryologically related neuroectodermal cells functioning as secretory units of peptide hormones produce proteins segments of which are structurally related.

Investigations have been made (in collaboration with Dr L. I Larsson Dept. of Biochemistry University of Aarhus Denmark and Dr F Sundler Dept. of Histology University of Lund, Sweden) to detect immunocytochemically PP-containing parenchymal cells in the islet organ of the hagfish, *Myxine glutinosa* and in the mucosa of the adjacent bile duct and gut, using antisera against APP and BPP Both "Bouin-fixed" and freeze dried or fresh frozen unfixed specimens have been studied but, so far no cells reacting immunochemically with PP antisera have been observed (unpublished observations) Immunocytochemical investigations aimed at a phylogenetical study of the occurrence of PP cells are rendered difficult due to two facts (*a*) that PP seems to show a rather marked species-specificity—to some extent illustrated in Table 1 and Fig. 2—and (*b*) that the hormone has still only been isolated from three species in three vertebrate groups mammals birds and reptiles (15 18) The evolutionary relationship between PP and insulin is highly interesting, considering the observations mentioned in the Introduction

PP and calcitonin

As also mentioned in the Introduction it was previously shown by statistical calculations that APP also showed another interesting correlation to bovine human and salmon calcitonins (Table 1 and Fig. 1) It suggests that under unusual circumstances calcitonin might also be present in the endocrine pancreas. As a matter of fact the production of calcitonin by islet-cell neoplasms has recently been described (2)

PP and VIP

An interesting connection between some other of these GEP hormones was indicated by the observations that segments 23–29 and 24–29 of BPP and APP respectively correlated well with segment 18–24 of VIP Moreover anoth-

HORMONE	SEQUENCE
GLUCAGON (12–17)	LYS TYR LEU ASP SER ARG
VIP (21–26)	LYS TYR LEU ASN SER TYR
b-CALCITONIN (14–19)	LYS ASP LEU ASN ASN TYR
b-CALCITONIN (14–19)	GLN ASP PHE ASN LYS PHE
s-CALCITONIN (14–19)	GLN ASP LEU HIS LYS LEU
APP (22–27)	ASP ASN [illegible] TYR
b-INSULIN (A) (14–19)	TYR GLN LEU GLU ASN TYR
hagfish INSULIN (A) (14–19)	TYR ASN (Gln) [illegible] TYR
h-p-b-PP (22–27)	ALA ASP LEU ARG ARG TYR
APP (14–19)	GLU [illegible] LEU [illegible] ARG PHE

Fig 3 Analysis of the charged sequence comparisons of VIP glucagon, PP calcitonin, and insulin. The search for possible progenitor sequence which is common to all these *statistically related sequences is shown. Specifically* the hexapeptide regions of APP *versus* salmon calcitonin, and APP *versus* hagfish insulin A chain are computed, based only on amino acid occurrence at each position within the hexapeptide indicated in the Figure. The phylogenetic relationship between these particular four sequences suggests that the progenitor sequence appears to have the structure: Glx Asx-Leu-Glx-Glx Tyr

er part (21–26) of the same VIP sequence matching the PPs contributes also to the correlation with sequence 14–19 of bovine calcitonin. The connecting links between charged segments of PP VIP and calcitonin (as well as glucagon see below) are important in detecting what could be a fundamental peptide unit (12) (see below)

VIP and the secretin family" (glucagon GIP)

The original observation that VIP is structurally related to glucagon and secretin (20) and also to GIP has led to the acceptance of a "family concept" for these hormones (5 25 32, 34) When the weakly charged segment (21–25) at the carboxy terminal of VIP is compared with a highly charged region from the center (region 12–16) of the glucagon molecule the probability of the match occurring by random chance is about 5×10^{-4} The important point is that the matching sequences are drawn from non-corresponding positions in the formal positioning of VIP and glucagon.

The match of non-corresponding charged segments from VIP (1?–16) with GIP (16–20) at a *P* value of 1.5×10^{-3} emphasizes that while some investigators view the glucagon-secretin-VIP-GIP "family concept" as well established (5 25 32, 34) the entire "family concept" requires re-evaluation (12)

The direct structural relationship between GIP and pro-glucagon discussed in detail in another publication (12) suggests that GIP may be physiologically linked to glucose homeostasis Indeed physiologically GIP is released by oral glucose (1) and is potently insulinotropic both *in vivo* and *in vitro* (33) Actually it has recently been claimed that its acronym should rather stand for "*G*lucose dependent *I*nsulinotropic *P*eptide" In adult onset diabetics glucose tolerance studies indicate that serum GIP levels are markedly more elevated in diabetic patients, following a glucose load, that they are in normal subjects (3)

VIP and glycoprotein hormones

The role of VIP in the hormonal inter-relationships found is most interesting and perhaps biologically relevant. VIP has recently been detected in brain synaptosomes and in nerves leading to the gastrointestinal tract (11 17) reinforcing the idea (11) that VIP has a physiological role as a neurotransmitter (26, 27) Our observation that 10 amino acids or 35% of the entire VIP structure correlates at a probability level of about 4×10^{-4} with a similarly sized charged sequence in the glycoprotein α-subunit would fit with the concept that VIP is not only involved in neurotransmission but is also related to the neural sites at which the β-subunits of the glycoprotein hormones thyrotropin (TSH) luteotropin (LH) and the follicle stimulating hormone (FSH) are produced in the anterior lobe of the pituitary As VIP also is found by epithelial cells of the GEP endocrine system, it is one of the most widespread and typical examples of how peptide endocrinology now seems to have become neuroendocrinology (see Introduction) In

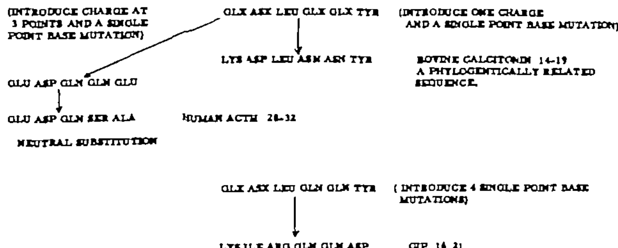


Fig 4 Possible derivations of the sequences of peptide hormones unrelated functionally to those hormones from which the possible progenitor sequence was deduced. Various mutations are attempted with the tentative progenitor sequence described in Fig. 3 The results suggested that charged sequences of calcitonin, ACTH and GIP could be obtained.

collaboration with Drs F Sundler and R. Håkansson at the Depts of Histology and Pharmacology University of Lund, Sweden, two of us (S O E & S F) have recently observed ample amounts of VIP in epithelial cells of the gut mucosa of cartilaginous fish (unpublished) indicating that epithelial VIP occurs fairly early in the evolution of the GEP endocrine system

Speculations on a progenitor peptide sequence

Thus it can be summarized that through a complex scheme of charged sequences VIP appears to be related to PP calcitonin glucagon, GIP and the α subunit of glycoprotein hormones Throughout the use of the primary sequences ("A protein") of VIP and APP described in seeking matches with target sequences in functionally unrelated sequences ("B proteins") one fact began to emerge quite distinctly As mentioned above it appeared that the target calcitonin sequence 14–19 of several species which is in the center of the highly variable region (14–27) of the calcitonin molecule, was related to penta- or hexapeptide regions of VIP and APP Moreover the same hexapeptide regions of VIP and APP and/or

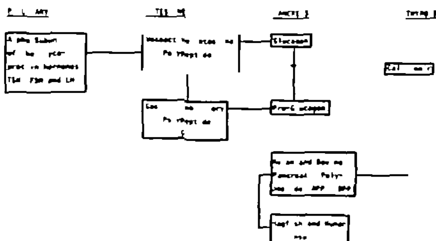


Fig 5 Sequence relationships between peptide hormones of the anterior pituitary the GEP endocrine system and the thyroid. The lines connecting the boxes indicate the connection by the statistical homologies described in the text.

BPP are related to each other as well (Table 1 sequences 4 and 5) This suggested that a fundamental or progenitor peptide sequence had been detected In order to evaluate and test this idea further all the related sequences of VIP APP glucagon calcitonin, and insulin were compared on a phylogenetic (codon relationship) basis (Fig. 3) A detailed analysis of the sequences appearing in Fig. 3 shows that these hexapeptide segments of differing peptide hormones are all related to each other at almost each corresponding position within the hexapeptide either by identity or single point base mutation. The sequences might, consequently be related phylogenetically

The supposition was now tested that some of these sequences were possible progenitors of charged sequences in other known hormonal peptides. In a classical evolutionary context it was decided to choose those sequences known to be related at various levels of probability from the lowest vertebrate orders specifically hexapeptide regions of APP *versus* hagfish insulin A-chain and APP *versus* salmon calcitonin. The result, based purely on the rate of amino-acid-residue occurrence at each position within the hexapeptide was. Glx Asx Leu-Glx-Glx Tyr Next various mutations were attempted by introducing a charge or single point mutations in this hexapeptide sequence The results suggested that charged sequences of calcitonin corticotropin (ACTH) and GIP could be obtained and the data appear in Fig. 4

Statistical hormonal peptide homologies and multiple-hormone-producing neoplasms

It is reasonably well accepted that the production of seemingly functionally unrelated peptide hormones by MEA-type tumor cells is a functional expression of cells derived embryonically from APUD-cells (22) As shown above a structural correlation exists between VIP and the α-subunit of the glycoprotein hormones (Fig. 5) VIP is present in lung parenchyma (28) and is also known to be produced by bronchial adenomas of carcinoid type (29) In view of the structural correlation between VIP and the α-subunit of the glycoprotein hormones the production of the latter by lung carcinoma would not be completely unexpected Oat-cell lung carcinoma has been reported to secrete the α-subunit of the glycoprotein hormones (14) Furthermore the structural correlation between VIP and calcitonin (Fig. 5) gives some aspects of the production of calcitonin that has also been observed by oat-cell carcinoma of the lung (30)

Finally the structural correlation between insulin PP VIP GIP and glucagon (Fig. 5) and the presence of seemingly functionally unrelated peptides in MEA, poses the question of whether two or more of these hormones could be produced by GEP tumor cells Whether one and the same GEP endocrine cell actually can produce more than one polypeptide hormone is still a matter of controversy (cf 7) but it is well known that one and the same GEP endocrine neoplasm often produces several polypeptide hormones such as insulin, PP glucagon, and VIP (16 24)

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(S. F) Department of Pathology
University of Umeå
S-901 87 Umeå
Sweden

PURITY AND ANTIGENICITY OF INSULIN PREPARATIONS

JØRGEN SCHLICHTKRULL

From the Novo Research Institute Copenhagen Denmark

Conventional insulin preparations are immunogenic, causing antibody formation against insulin and a number of pancreatic hormones and proteins. The circulating antibodies react with the corresponding immunoreactive components in the preparations, and antigen-antibody complexes are formed which may cause allergy elevated dose requirements or resistance possibly local lipoatrophy and other cell damage.

The observation made in rabbit immunization experiments that non-insulin components isolated from conventional crystalline insulin elicited very high levels of circulating insulin antibodies inspired testing an insulin devoid of contaminants and this insulin was found to be non-immunogenic (6 7)

In 1970 MC insulin was made available for therapy MC is short for "monocomponent" which signifies the removal of all components other than insulin itself The heterogeneity of once crystallized insulin is illustrated in Fig. 1 The curve represents gel filtration separating according to molecular size and the patterns obtained by disc electrophoresis relate to fractions isolated as indicated by the broken lines

Analyzed by this method, MC insulin would show one peak (c) and display one band after electrophoresis MC insulin is further characterized by quantitative specifications e.g. since 1974 it contains less than 0.0001% (by weight) of proinsulin-like substances as determined by radioimmunoassay (11) Its potency is assumed at 169 MU/mol, i.e. 185 U/mg of nitrogen or about 27 U/mg (the material contains some water and salts) (12) It is to be understood that the specifications apply to the insulin from which the MC insulin preparations are made. In the course of storage a few percent deamidation and insulin polymerization may occur (10) Neither the stored preparation nor the isolated transformation products were immunogenic in rabbit immunization experiments (9 10) Thus, the insulin transformation products do not have the immunogenic characteristics of the contaminants removed in the preparation of MC insulin.

To obtain MC insulin, a series of chromatographic steps has been introduced in the purification process for the separation of molecules not only on the basis of their different sizes but also according to differences in their ionic charge (9) Chromatography is now also used by most American and Continental West European insulin manufacturers Single Peak Insulin is produced in the US by gel filtration and, like the German "Chromatografisch gereinigtes Insulin" it is not purified by ion exchange chromatography (4 17)

The claims of purity for MC insulin have been challenged by some investigators whose papers are being referred to as controversial evidence and—left uncommented—may cause some confusion. One example is the article by Yue and Turtle (15) According to their statements they analyzed MC insulin using Sephadex gel chromatography and found two peaks (Fig. 2, broken-line curve) Peak I estimated to represent 5% of the total protein,

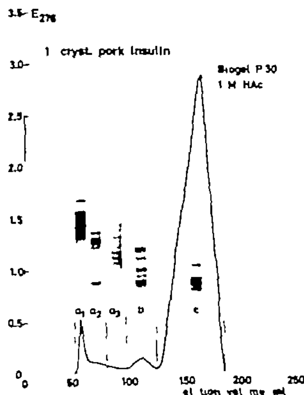


Fig 1 Gel filtration of once crystallized pork insulin on Biogel P 30. The disc electrophoresis was carried out after rechromatography of the individual components. The bands of the c-peak are from top down arginine-insulins plus insulin ethyl esters, the insulin, and monodesamidoinsulin. The three most prominent bands of the b-component are, from the top down: proinsulin, the intermediates and the dimer None of the bands of the a_1, a_2 or a_3-components has been identified, the a_1 containing a series of slowly migrating bands and a smear on the disc electrophoresis. (These data were first published in *Horm Metab Res* Suppl. Vol. 5 134 1974. Reproduced by courtesy of the Editors.)

was assumed to consist mainly of covalently linked insulin dimer with electrophoretic properties similar to those of insulin. Unfortunately a pharmaceutical MC insulin preparation was used as starting material (16) It contains a strongly UV absorbing preservative methylparahydroxybenzoate, which causes a big Peak II when gel filtered according to the method of Yue and Turtle as shown in Fig 2 which depicts the Yue and Turtle data, broken line, and the transmission data obtained in our laboratory (5) with 9 ml U-80 Actrapid® MC using the Yue and Turtle techniques. Peak II caused by the preservative was mistakenly believed by the authors to represent insulin If Peak II had been due to insulin it would have corresponded to more than 10 times the amount of insulin stated for analysis (100 mg) The authors do not explain how they calculated the relative amount (5%) of Peak I protein It is true that the peak I area below the transmission curve is 5% of the total area but then the calculation is meaningless since it should be based on extinction and not on transmission. It is evident that the qualitative identification of the high-molecular weight protein (M>6000) was false and the calculation of quantity meaningless.

Another example is an article (1) in which the authors suggested that MC insulin contained proinsulin or another antigen because it formed two precipitin lines after diffusion (Ouchterlony technique) against serum from guinea pigs immunized with conventional insulin. We have reproduced the analysis (8) with the result shown in Fig. 3 Regardless of purity the insulin produced a second band In another run Zn insulin complexes were dissociated with 1 mM EDTA (in all solutions) and the "proinsulin" line disappeared, as shown in Fig. 4

A true proinsulin line in this system is shown in Fig. 5 The lines fused i e. the method does not discriminate between insulin and proinsulin and consequently cannot be

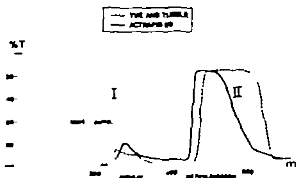


Fig 2 Gel chromatography (Sephadex G 50 1 M HAc) of 9 ml Actrapid 80 MC containing total of 100 mg dry substance. UV absorption at 254 nm vs. elution volume recorded with an LKB U icord (solid line).

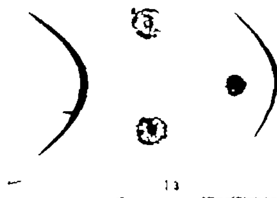




Fig. 3 Passive immunodiffusion of once crystallized pork insulin (top, left) and MC insulin (top, right) against anti-insulin guinea-pig serum (bottom well)
Fig. 4 Same as Fig. 3 but with 1 mM EDTA.

Fig. 5 Passive immunodiffusion of pork MC insulin (top left) and pork proinsulin (top, right) against anti-insulin guinea-pig serum (bottom well) with 1 mM EDTA.

used for the determination of proinsulin in insulin preparations. It is evident that the "proinsulin" line has been a methodological artefact ascribable to Zn insulin complexing. A similar phenomenon is known from electrophoresis (13)

The radical removal of protein contaminants prevents the formation of antibodies to the so-called pancreatic polypeptide or PP glucagon, and the gut hormone VIP Bloom and co-workers found PP and VIP in conventional preparations but not in MC insulin preparations. In patients on conventional insulin, they found some to have developed antibodies against PP glucagon or VIP whereas such antibodies were absent in patients who had been treated only with MC insulin (3)

Likewise new-on-insulin patients developed antibodies against a-component protein only when treated with conventional preparations (14) Similar results were obtained with regard to proinsulin antibodies that do not react with insulin (14)

Insulin antibody formation was markedly reduced in patients treated with MC insulin, regardless of species. It is concluded that immunoreactive insulin found in contaminating protein acts as a hapten (14)

The term antigenicity covers two properties, viz. *immunogenicity* and *immunoreactivity*. Even if an insulin preparation is not immunogenic, i.e. it does not induce antibody formation, the insulin will possess immunoreactivity i.e. it will be bound by the insulin antibodies already present from previous treatment with an immunogenic insulin preparation.

The circulating *insulin-antibody* complex is destroyed by the liver and this elimination of insulin adds to the dose requirement so that it will exceed the requirement in the absence of insulin antibodies (7) In general the amount of bound insulin and the increment in dose requirement are greater with bovine insulin than with porcine insulin A sudden decrease in dose requirement due to immunological reactions such as the decrease occasionally seen after a change from conventional beef/pork insulin to MC pork insulin is therefore not a question of purity or immunogenicity but of species

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Table 1 *Effects of glucose on (^3H) cyclic AMP accumulation in 1–5 min incubations*

0.1 mM IBMX was included in all incubation media. Mean ±S.E.M. of 5 experiments

Glucose (mM)	Incubation time (min)	(^{3}H) cyclic AMP (dpm/islet)
3.3	0	4.8±0.7
3.3	5	4.2±0.4
27 7	1	9 1±1 4
27 7	2	11 0±1 4
27 7	3	11 0±1 1
27 7	5	11 7±0.9

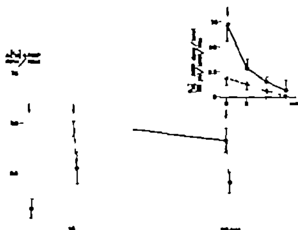


Fig 1 Time-course of the effect of 27 7 mM glucose on islet (^3H) cyclic AMP accumulation (main figure, *n*=6). At different time intervals (arrows) the medium was changed to 3.3 mM glucose and (^{3}H) cyclic AMP measured after another 2 min incubation (interrupted lines). In separate experiments (insert, *n*=4) all islets were incubated for 60 min with 27 7 mM glucose and then incubated in 3.3 mM glucose for the times indicated, the islets being transferred to new incubation medium with 3 min intervals and (^{3}H) cyclic AMP (●) and insulin (▲) measured. The insulin secretion rates were calculated from the insulin accumulated during each 3 min period. 0 1 mM IBMX was included in all incubation media. All results are expressed as mean ±S.E.M. of values after subtraction of the appropriate controls. (Reproduced from Grill and Cerasi 1977)

measurable effect on insulin release (12) However the batch-type incubations employed here (where insulin release is accumulated in the incubation media) are not ideal for measuring moment-to-moment changes in insulin secretion. In perifused islets the time of onset for cyclic AMP and insulin responses were identical (9) It thus seems safe to conclude that cyclic nucleotide stimulation at any rate, is not a phenomenon that takes place secondary to the insulin release process

The time-course of the glucose effect on (^{3}H) cAMP over a 60 min period is shown in Fig 1 cAMP increases rapidly up to a plateau after which the level of intracellular nucleotide declines slowly In the experiments shown a low concentration of the phosphodiesterase inhibitor 3-isobutyl 1 methyl-xanthine (IBMX) was included in order to augment the cAMP responses. In the absence of IBMX, the decline was somewhat more pronounced, islet (^{3}H) cAMP in some experimental series not being significantly elevated after 60 min of stimulation with glucose (3) Under all conditions a substantial release of cyclic nucleotide occurred progressively with time during stimulation with glucose (3) Figure 1 shows further that the stimulation of cAMP is reversible when the glucose stimulus is withdrawn and that the decline of the cyclic nucleotide occurs wholly in parallel to the cessation of insulin release.

When different concentrations of glucose (0–27 7 mM) were tested in 3 min incubations in the presence of 0 1 mM IBMX (Fig. 2) the threshold concentration for eliciting a cAMP response was between 5 0 and 6 6 mM A half maximal response was obtained with approximately 8.3 mM and a maximal response with 27 7 mM of glucose. These dose-response

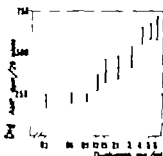


Fig 2 Dose-response relationship for the effect of D-glucose in the presence of 0.1 mM IBMX on the islet accumulation of (^{3}H) cyclic AMP in 3 min incubations. Mean ±S E.M. of 7 experiments. (Reproduced from Grill and Cerasi 1974.)

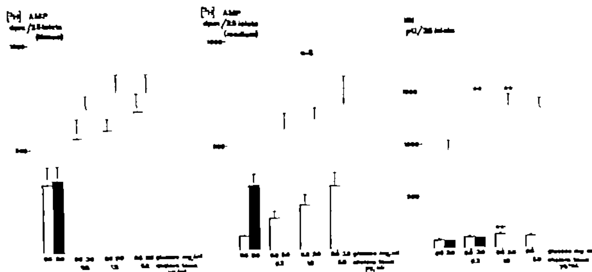


Fig. 3. Effects of cholera toxin on (^{3}H) cyclic AMP in islets and incubation media and insulin release after 60 min of incubation in the absence or presence (hatched columns) of 3.0 mg/ml of glucose. ** = $P<0.01$ and * = $P<0.05$ for the effects of cholera toxin.

characteristics are not obviously different from those observed for insulin release (3, 12); in particular both insulin and cAMP responses were absent below a similar threshold concentration of glucose (Table 2).

All the findings presented above show a parallelism between glucose-induced stimulation of cAMP and insulin secretion. A close association was also found between the efficiency of analogs, isomers and epimers of D-glucose to stimulate or inhibit each of the two parameters (4, 5). Altogether, this evidence strongly indicates that the cyclic nucleotide plays an important role in mediating the glucose action on insulin release.

Granted the importance of cAMP, it is clear that the idea of this nucleotide being the sole mediator of glucose action is not easily reconciled with all experimental evidence. A limited role for cAMP is suggested from experiments in which the islet cAMP level was elevated with high concentrations of phosphodiesterase

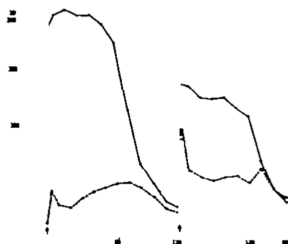


Fig. 4. Insulin responses to two successive stimulations with glucose (↑—) in a healthy volunteer. Horizontal axis denotes min of observations, vertical axis insulin (μU/ml) or glucose (mM) recorded. — = glucose, –·– = insulin values.

Table 2. *Effects of glucose (0–8.3 mM) on islet (^{3}H) cyclic AMP and insulin release measured simultaneously in 10 min incubations*

0.1 mM IBMX was present in all incubations. Mean ±S.E.M. of 4 experiments

Concentration of glucose (mM)	(^{3}H) cyclic AMP (dpm/islet)	IRI (μU/islet)
0	8.9±1.6	1.8±0.5
3.3	8.5±1.3	2.3±0.8
8.3	1[illegible]4±2.5	9.2±[illegible]

Table 1 *Effects of glucose on (³H) cyclic AMP accumulation in 1–5 min incubations*

0 1 mM IBMX was included in all incubation media. Mean ±S.E.M. of 5 experiments

Glucose (mM)	Incubation time (min)	(³H) cyclic AMP (dpm/islet)
3.3	0	4.8±0.7
3.3	5	4.2±0.4
27 7	1	9 1±1 4
27 7	2	11 0±1 4
27 7	3	11.0±1 1
27 7	5	11 7±0.9

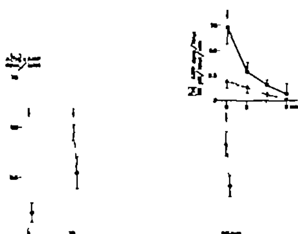


Fig 1 Time-course of the effect of 27 7 mM glucose on *islet (³H) cyclic AMP accumulation (main figure, n=6).* At different time intervals (arrows) the medium was changed to 3.3 mM glucose and (³H) cyclic AMP measured after another 2 min incubation (interrupted lines). In separate experiments (insert, n=4) all islets were incubated for 60 min with 27 7 mM glucose and then incubated in 3.3 mM glucose for the times indicated, the islets being transferred to new incubation medium with 3 min intervals and (³H) cyclic AMP (●) and insulin (▲) measured. The insulin secretion rates were calculated from the insulin accumulated during each 3 min period. 0.1 mM IBMX was included in all incubation media. All results are expressed as mean ±S.E.M. of values after subtraction of the appropriate controls. (Reproduced from Grill and Cerasi 1977)

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When different concentrations of glucose (0–27 7 mM) were tested in 3 min incubations in the presence of 0 1 mM IBMX (Fig. 2) the threshold concentration for eliciting a cAMP *response was between 5 0 and 6.6 mM.* A half maximal response was obtained with approximately 8.3 mM and a maximal response with 27 7 mM of glucose. These dose-response

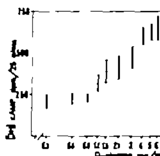


Fig 2. Dose-response relationship for the effect of D-glucose in the presence of 0.1 mM IBMX on the islet accumulation of (³H) cyclic AMP in 3 min incubations. Mean ±S.E.M. of 7 experiments. (Reproduced from Grill and Cerasi 1974.)

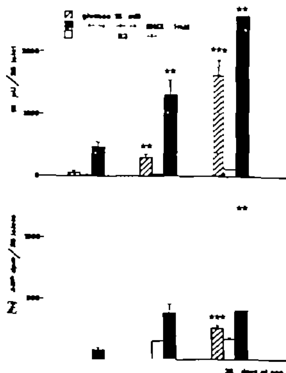


Fig 5 Effects of glucose 16.7 mM on islet (^{3}H) cyclic AMP (measured after 3 min incubations, —Q) and insulin release (measured after 60 min incubations, —5). *** ** * = $P<0.001$, $P<0.01$ and $P<0.05$ significance of the glucose effect. (From Grill and Cerasi 1975*b*)

the hexose being unaffected by the drugs. The close relationship between glucose and sulfonylurea in respect to insulin release indicates that the mode of action of sulfonylurea could be related to that of the hexose. A common denominator for both agents could be the islet cAMP Indeed it has been shown that tolbutamide stimulates the accumulation of cAMP and insulin release with the same time kinetics (1) We have found that sulfonylurea (tolbutamide and glibenclamide) in parallel with their insulin releasing action have effects on (^{3}H) cAMP at low but not at high concentrations of the hexose (Table 4) Altogether these results suggest that cAMP is an important factor in mediating the secretagogic action of sulfonylurea and that possibly the drugs act at the same cAMP stimulating site as glucose. Presently available evidence is insufficient to determine decisively whether this site is the islet adenylate cyclase or some other step of cAMP metabolism in the beta-cell

The role of cAMP in physiological and pathophysiological states characterized by decreased insulin release

Fasting and the neonatal period of life are two well studied conditions in which the insulin response to glucose is decreased. The cAMP response to glucose is likewise hampered under these conditions although a complete parallelism with the pattern of insulin release is not obtained (5 12 Fig. 5) Diabetes in the Chinese hamster is accompanied by decreased insulin release and an obliterated cAMP response compared with normal animals of the same species (13) Altogether these results indicate that a decreased cAMP response could well be involved in the observed secretory defects. Much further research is obviously needed in order to define clearly whether the cAMP stimulating effect of glucose and/or other actions of the hexose are of major importance in the various conditions associated with decreased insulin release.

ACKNOWLEDGEMENTS

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Department of Endocrinology
Karolinska Hospital
S-104 01 Stockholm 60
Sweden

DISCUSSION

Anders Widström Cerasi and Luft have suggested that low insulin response is a marker for diabetes Definitely increased incidence of (maturity onset) manifest diabetes among the low responders would be a final proof of the correctness of the hypothesis You mentioned that an increased frequency of diabetes had been found among the low responders Is this correct?

Valdemar Grill The occurrence of diabetes among low responders in comparison with high responders is not known However there is evidently a greater incidence of latent diabetes among the low responders than among the high responders (Cerasi E & Luft, R. Follow-up on non-diabetic subjects with normal and decreased insulin response to glucose infusion—first report. *Horm Metab Res* Suppl. 5 113 1974)

Yngve Larsson I am surprised at this statement Dr Grill To my knowledge it has not yet been possible to demonstrate any clinical differences whatsoever between low-responders and high-responders

Anders Widström Since it is well known that the glucose tolerance varies in each subject and since low-responders as a group from the time of identification have lower glucose tolerance than high-responders the finding of a higher prevalence of latent diabetes among low-responders seems to be a very incomplete argument for the importance of the low insulin response for the development of (maturity onset) manifest diabetes mellitus

Valdemar Grill It is known from the literature (Fajans et al. Some aspects of the natural history of diabetes mellitus. *Diabetes* Proc of the 8th Congress of the International Diabetes Federation, Excerpta Medica, Amsterdam 1974 pp. 329–340) that people with latent diabetes have a tendency to develop overt diabetes mellitus

Anders Häger I have a question about the increased insulin sensitivity of the liver in prediabetes Is anything known about the mechanisms regarding the progress from increased to normal or decreased sensitivity when clinical diabetes emerges?

Valdemar Grill Not as far as I know

Niels Schwartz Sörensen. I have a comment on the changes of insulin sensitivity in the liver These changes might very well be induced by alterations in the properties and concentration of insulin receptors of the liver cells. Furthermore I should like to have your comment concerning the action of sulfonylureas on the beta cells. As far as I know these compounds are unable to penetrate the cell membrane. Do you think that sulfonylureas exert their well known effect outside the cell eventually via the cell membrane?

Valdemar Grill Regarding the first question. It is clear from numerous studies *in vivo* and *in vitro* that the concentration and affinity of insulin receptors in different organs can vary with different metabolic states. In particular the number of insulin receptors seems to be inversely related to the prevailing concentration of insulin. Regarding the second question. Hellman et al. have shown that sulfonylurea does not readily penetrate the beta cell membrane (Hellman et al. *Biochem Biophys Res Commun 45* 1384 1971 Hellman et al. *Diabetologia* 9 210 1973) These findings do support the idea that sulfonylurea exert their effects at the cell membrane.

HUMAN PROINSULIN IN INSULIN TREATED JUVENILE DIABETICS

L. G. HEDING and J. LUDVIGSSON

From the Novo Research Institute, Copenhagen, Denmark, and Department of Pediatrics, Linköping University, Linköping, Sweden

ABSTRACT Human proinsulin was determined in a group of 73 diabetics, aged 5–20 years, with onset of diabetes at the age of 1–16 years and a duration of diabetes of 2–17 years. At the time of the investigation, the patients were receiving conventional 3 times crystallized insulin and all had detectable insulin binding IgG. Because of the binding of human proinsulin to insulin antibodies the serum was extracted with acid ethanol. Proinsulin was then determined in fasting serum after removal of human C-peptide which would have interfered with the proinsulin radioimmunoassay. The detection limit in normal serum not containing antibodies was 0.01 pmol/ml. The detection limit in sera that had to be extracted was approximately 0.05 pmol/ml. 31 of the patients (42%) had detectable serum proinsulin, ranging from 0.055 to 2.00 pmol/ml. In the same group of patients, 19 (26%) had detectable C-peptide. There was a strong correlation between the concentration of human proinsulin and C-peptide ($P<0.001$). 38 normal fasting sera contained from 0 to 0.033 pmol/ml, mean ±S.D.: 0.009±0.008 pmol/ml. The human proinsulin constituted from 0.1 to 92% of the total immunoreactive insulin (IRI) in the 31 patients with detectable proinsulin (mean: 8.5%). Thus it appears that proinsulin was secreted in 42% of 73 insulin treated juvenile diabetics who had had diabetes for 3–14 years, whereas C-peptide was found in 26% of the patients. The insulin antibodies bind a portion of the secreted proinsulin, prolonging its half-life and increasing its serum concentration. Hence, the levels of proinsulin in patients having insulin antibodies are not comparable to those in persons without antibodies.

KEY WORDS: Juvenile diabetes, insulin, C-peptide, proinsulin, insulin antibodies

C peptide and insulin are secreted from the B-cell in equimolar amounts together with a few percent (mole %) of proinsulin (12) that for some unknown reasons has not been split enzymatically into C peptide and insulin. Provided that C peptide has the same half-life in insulin-treated diabetics as in normals measurement of serum C peptide is a source of information on the function of the B-cell in these patients. Several papers have now been published demonstrating the value of C-peptide determinations for monitoring the B-cell function in the insulin treated patient (1 2, 8 13) C peptide was found in a group of 96 insulin treated juvenile diabetics (14) and in a recent study residual CPR (C peptide immunoreactivity) was found in 71% of 35 juvenile diabetics (6) However in the latter study human proinsulin was not removed prior to the determination of C peptide and this may have resulted in an overestimation of the C peptide values It has been reported that human proinsulin may constitute an extremely high proportion of the CPR in insulin treated diabetics in all probability mainly because of the binding of proinsulin to the insulin antibodies (2, 4 10) The purpose of the present study was to determine the concentration of human proinsulin in a group of insulin-treated juvenile diabetics and to compare the results of this study with the results obtained in a group of adult insulin requiring diabetics (11)

MATERIALS AND METHODS

The separation of C-peptide and proinsulin is shown in Fig. 1 Purified insulin antibodies were covalently coupled

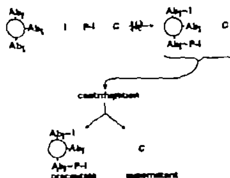


Fig. 1. Principle of separation of proinsulin and C-peptide.

to Sepharose (S-AIS) (9). T 1 ml of serum or of serum extract containing insulin, proinsulin and C-peptide, was added 100 µl of a S-AIS suspension with a binding capacity of 0.01 U/ml. After shaking at 4°C for 24 h, all the molecules containing an insulin moiety were bound to the S-AIS.

The supernatant containing the free C-peptide was then assayed as described previously (9). The S-AIS-bound proinsulin was assayed directly while bound to the solid-phase antibodies (10), using human proinsulin as the standard (kindly donated by Professor Arthur Rubenstein of Chicago) and ^{125}I-labelled synthetic Tyr-C-peptide as the tracer (15). The detection limit in unextracted serum was 0 01 pmol/ml, it was 0.05 pmol/ml in serum that had been extracted. The immunoreactive insulin (IRI) in serum containing insulin antibodies was determined after acid extraction (7) and insulin binding IgG according to the immunoelectrophoretic separation method of Christiansen (3).

Our patient material consisted of 73 insulin treated juvenile diabetics (36 girls and 37 boys) aged 5–20 years who had had diabetes for 2–17 years. All patients attended the Diabetic Clinic of the Pediatric Department regularly 4–8 times year. At the time of this investigation, the patients were on conventional 5 times crystallized insulin preparations. Blood samples were taken from fasting patients prior to the morning insulin injection, and the serum was stored at −18°C until assayed.

Table 1. *Proinsulin in 73 insulin-treated juvenile diabetics pmol/ml*

	<0.05	>0.05	0.055–0.100	>0 100–0.500	>0.500–2.00
Boys	19	18	9	7	2
Girls	23	13	7	4	2
Total	42	31	16	11	4
%	58	42	22	15	5

RESULTS

Proinsulin in fasting normals and insulin-treated juvenile diabetics

Table 1 shows that 31 of the patients had detectable proinsulin amounting to 0.055–2.00 pmol/ml. In fasting sera from 38 normal subjects, proinsulin ranged from 0–0.033 pmol/ml, mean ±1 S.D 0 009±0 008 pmol/ml (own observations)

C-peptide total IRI and insulin antibodies in patients with and without proinsulin

A strongly positive correlation was found between the concentration of C-peptide and proinsulin ($P<0.001$) The values of C-peptide, total IRI and insulin binding IgG in the patients with and without proinsulin are shown in Table 2. All patients had detectable insulin binding IgG ranging from 0 106 to 11 029 mU/ml, and the range of total IRI was 42–9 120 µU/ml.

Human proinsulin in relation to the total IRI and C-peptide

Human proinsulin reacted in the IRI-assay to approx. 66% on a molar basis in other words 0.5 pmol/ml reacts as 50 µU/ml of insulin. Table 3 shows that human proinsulin constituted 0.1–92% (mean 8.5%) of the total IRI and Table 4 shows the calculation in the 10 patients having a proinsulin concentration higher than 0.025 pmol/ml.

C-peptide was detected in 19 of the 73 diabetics (>0 03 pmol/ml) 26% Of the 31 patients having detectable proinsulin, 16 also had

Table 2. *C peptide total IRI and insulin binding IgG (mean ±1 S.D) in insulin treated juvenile diabetics*

Proinsulin (pmol/ml)	C-peptide (pmol/ml)	Total IRI (µU/ml)	IgG binding (mU/ml)
<0.05 (42)	0 023±0.018	779±1 254	2.39±2.19
>0 05 (31)	0.21 ±0.43	1 436±1 867	3.12±3.14

Table 3 *Human proinsulin in % of total IRI in 31 insulin-treated juvenile diabetics*

	Proinsulin (pmol/ml)	Total IRI (μU/ml)	Proinsulin (% of IRI)
Range	0.055–...00	93–9 121	0.1–9?
Mean	0.334	1 436	4.5

C peptide In 29 of the patients the concentration of the proinsulin was higher than that of C peptide Proinsulin constituted from 37–100% of the sum of proinsulin and C-peptide on a molar basis with a mean ±1 S D of 70±16%

DISCUSSION

It has been demonstrated using gel filtration of the acid serum extract, that human proinsulin constituted the major portion of CPR in 4 adult-onset insulin-treated diabetics (2) Recently this finding was confirmed using a specific direct radioimmunoassay for proinsulin (10) in a group of 24 adult insulin-requiring diabetics all of whom had circulating human proinsulin ranging from 0 1 to 9 4 pmol/ml—values far higher than the C peptide which was found in only 3 patients (11) There are several reasons why the determination of proinsulin in sera from insulin-treated diabetics is so important. First of all the use of the C peptide assay in monitoring the B-cell function with respect to insulin secretion becomes invalid if proinsulin is present in concentrations far higher than those of C peptide This is because proinsulin crossreacts in the C peptide assay Second it is of obvious interest to measure the concentration of the precursor of insulin—proinsulin—in diabetics It has been observed that in some types of diabetes the percentage of proinsulin was higher after oral glucose (5 16) In insulin requiring diabetics with virtually no IRI increase after oral glucose the % of proinsulin increased from a mean fasting value of 16 to 31% in contrast to normals in whom the values dropped from 19 to 8% (10) Thus the B-cell of the insulin requiring diabetic may secrete too high a percentage of proinsulin in response to stimuli

The present results showed the presence of human proinsulin in 42% of 73 juvenile diabetics who had had diabetes for a duration of 2–17 years In contrast C-peptide was found only in 26% of the patients Moreover the concentration of proinsulin was higher than that of C peptide in all but two patients Hence it can be concluded that insulin secretion in insulin treated diabetics cannot be monitored using the C peptide assay unless proinsulin has been removed

The quantitation of proinsulin in these juvenile diabetics does however provide supplementary information about the B-cell function. Thus 42% of the patients in this study had retained some proinsulin biosynthesis and secretion even though C peptide could not be detected in some of these patients This was considerably less than in 24 adult insulin requiring diabetics in whom all the 24 patients had proinsulin levels >0 1 pmol/ml. The explanation of the discrepancy may be that the present study was concerned with the young diabetics who probably retain the B-cell activity for a shorter period of time The high concentrations of proinsulin found in the 31 patients all of whom had insulin antibodies cannot be compared with the values found in persons without antibodies Antibodies bind

Table 4 *Proinsulin and total IRI in 10 insulin-treated juvenile diabetics with proinsulin >0.025 pmol/ml*

Patient no	Proinsulin (pmol/ml)	Total IRI (μU/ml)	Proinsulin (% of IRI)
4	1 9?	710	27
10	0.54	451	12
4	0.48	259	19
3_	0 40	3 072	1.3
34	2 00	2 750	7.3
41	0 27	173	16
46	0 41	275	15
54	1 65	179	92
55	0 44	182	4
86	0.36	326	8

proinsulin prolong its half-life and consequently increase its serum concentration to values much higher than they would be in the absence of antibodies

This circumstance makes it difficult to calculate the secretion rate of proinsulin or the ratio of secreted proinsulin to C-peptide. The latter would provide information to show if the percentage of secreted proinsulin is abnormally high However it appears that the measurement of proinsulin may provide the possibility of following the function of the B-cell even longer than by the determination of C-peptide.

When proinsulin was calculated in percent of the total IRI which comprises exogenous and possibly endogenous insulin and proinsulin the values found varied from 0 1 to 92% mean 8.5% In patients in whom proinsulin constitutes more than, e g. 15% of the total IRI it seems likely that the secretion of proinsulin in relation to insulin is higher than normal unless the insulin antibodies bind proinsulin more avidly than insulin. This problem cannot be solved until a well defined tracer of human proinsulin has been prepared and its half-life determined in diabetic patients with antibodies.

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(L. G. H.) *Novo Research Institute*
Novo Allé
Dk 2880 Bagsvaerd
Denmark

DISCUSSION

Claes Hellerström A recent report by Gabbay et al. (*Diabetes 24* Suppl 2, 413 1976) describes a family with inherited proinsulinemia probably reflecting a defective conversion of proinsulin to insulin. None of the family members were however diabetic My question is whether you have measured proinsulin in the blood of your juvenile diabetic patients with increased circulatory proinsulin?

Lise Heding No we have not done this kind of investigation as yet.

Jørgen Schlichtkrull Are there two populations of granules one containing proinsulin and the other insulin and are these secreted separately? Perhaps Dr Hellerström could comment on that?

Claes Hellerström Most evidence suggests that mature secretion granules contain insulin, C-peptide and a small amount of proinsulin. Steiner et al (*J Clin Invest 51* 1476 1972) have also shown that newly formed secretion granules containing higher ratios of proinsulin to insulin mix with a pool of preexisting storage granules and are secreted with these in a random fashion

Sture Falkmer I think a piece of supplementary information is needed to Dr Hellerström s answer about the homogeneity of the secretion granules in mammalian beta cells In our laboratory we found almost 10 years ago that when the sulfide silver procedure is applied on an ultrastructural level to detect the presence of heavy metals notably zinc in the islet parenchymal cells a marked difference could be observed between the secretion granules close to the Golgi apparatus and those distant from it. The latter contained more heavy metals than the Golgi-associated granules—a finding that was interpreted as a maturation process (Falkmer and Pihl *Diabetologia 4* 329 1968) Thus some heterogeneity can be observed in the beta granules.

Ivar Følling Your diabetics may release insulin and proinsulin in a normal ratio The half life of C peptide in the blood is short, and that of proinsulin bound to antibodies is much longer and probably highly variable within patients Therefore the levels of C peptide and proinsulin do not reflect their relative secretion rates

Lise Heding I cannot exclude the possibility that proinsulin and insulin are secreted in a normal ratio However if this is the case then we have to assume that the antibody-bound insulin has a much shorter half-life than the antibody-bound proinsulin to explain why proinsulin constitutes so high percentages of the total IRI

Anders Widström Have you not tested an in vitro system? In vitro you could easily vary the rates of insulin synthesis and release and see if the proportion of proinsulin/insulin is related to these rates

Lise Heding The problem in this connection is that the assays for C-peptide and proinsulin are species specific In order to work with the rat islets we would need an assay for rat C peptide

C PEPTIDE IN JUVENILE DIABETES

J LUDVIGSSON and L. G. HEDING

From the Department of Pediatric University Hospital Linköping Sweden,
and Nov Research Institute Copenhagen, Denmark

ABSTRACT C-peptide can be used as measure of endogenous insulin secretion in insulin treated diabetics with insulin antibodies. At the onset of juvenile diabetes insulin production is thought to be absent or minimal, but we have found rather high levels of C-peptide, even in ketoacidotic patients. The ketoacidosis does not mean an irreversible beta cell failure. In the postinitial remission period with stable metabolism many patients have normal or almost normal C-peptide levels and their beta cells have the capacity to respond to natural stimulation with an increased insulin secretion. For some unknown reason the metabolism becomes more labile coinciding with decreasing C-peptide values. However even several years beyond the postinitial remission period many juvenile diabetics have some persistent beta cell function, and it has been shown that even trace remnants of beta cell function are of importance for stabilization of the metabolism. There is no reason to believe that the beta cell failure should be predetermined e.g. by genetic factors. However little is known how to influence the progression and stop the increasing beta cell failure. Some of our results suggest that an early detection and an intensive treatment of diabetes before severe metabolic disturbances and pronounced insulin deficiency have appeared, may increase the possibility of preserving some beta cell function.

KEY WORDS: Juvenile diabetes, insulin, C-peptide, proinsulin, insulin antibodies, remission, metabolic control

Juvenile diabetes mellitus is a disease of insulin deficiency This has been confirmed by the immunoassay for the determination of insulin (2, 23 34 47) Studies on the pathological changes in the pancreatic islets support the concept of a primary failure of the beta cells (17 18) The defects may involve the production (52) and the secretion of insulin (9 10 11 20 42, 49) as well as the regeneration of the beta cells (19) In recent years methods for the determination of C-peptide have made it possible to study the endogenous insulin production even in juvenile insulin-dependent diabetics with circulating insulin antibodies (44)

STRUCTURE AND MEASUREMENT OF C-PEPTIDE

In 1967 Steiner et al (50) found evidence of a precursor of insulin, called proinsulin (Fig. 1) which on insulin release is split into insulin and the "connecting peptide" built up of 31 amino acids The C-peptide is secreted together with insulin in equimolar amounts (7 30) and the relation between insulin and C peptide is 1 1 in the portal vein. However this ratio is 1 5–15 in peripheral blood (30) which can be explained by the lever extraction of insulin while C peptide traverses the liver and is removed by the kidneys (33). Measurement of plasma disappearance halftime (T 1/2) has been found to be 2–3 times longer for C-peptide than for insulin (29 35) In peripheral blood C-peptide may reflect beta cell function better than insulin itself

Since antibodies reacting with C-peptide also react with proinsulin (Fig. 2) it is necessary to remove proinsulin before the determination of C-peptide (30) especially as juvenile diabetics may have relatively high proinsulin values (41)

The method described in the paper by Lise

Fig 1 The porcine proinsulin molecule according to Chance and coworkers.

Heding (26) means that insulin antibodies bound to Sepharose react with insulin and proinsulin. After centrifugation C peptide remains in the supernatant and can be measured without interference from the proinsulin The detection limit (that is the lowest concentration that is significantly above zero) is approximately 0 02 pmol/ml The specificity with the antiserum used (M 1181) is very high (16)

C PEPTIDE IN CHILDREN WITH JUVENILF DIABETES

At the onset of juven le diabetes at least in ketoacidotic patients n ulin production is said to be absent or mnimal (3 45) Block et al (6) found no C pept de in 5 of 6 ketoacidotic patients at the onset but ~20 weeks later while still receiving nsulin therapy all patients had evidence of beta cell secretory activity This was assessed by C peptide immunoreactivity (CPR) which includes both C peptide and part of the proinsulin. Thus the occurrence of ketoacidosis does not necessarily mean total irreversible beta cell failure In some juvenile diabetics with clinical signs of postinitial remission Beischer et al (3) found normal serum fasting C peptide levels. Other authors have reported similar results in adults with insulin dependent diabetes of short duration (7 13 14 15 26)

react with Ab against C-peptide alone

insulin proinsulin C-peptide

react with Ab against insulin alone

Fig 2 Antibodies against C-peptide will react with both C-peptide and proinsulin.

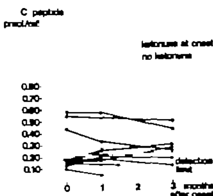


Fig. 3. Serum C-peptide levels in 10 juvenile diabetics on admission to hospital (time 0) and fasting values 1–3 months after onset.

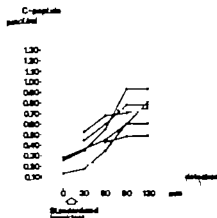


Fig. 4. C-peptide response to a standardized breakfast 3 months after onset in 6 children with juvenile diabetes in postinitial remission.

During the past year we have determined fasting serum C-peptide at certain intervals from the onset of diabetes in 10 children. Age at onset varied between 4–16 years (8.9±4 4) All but one had ketonuria at onset, but no patient had severe ketoacidotic symptoms. On admission to the hospital before any insulin had been given, these patients had remarkably high C peptide levels as shown in Fig. 3 It should be noted that these values are not fasting values but represent the maximal capacity of the beta cells under stimulation from high blood glucose levels (range 16.0±48 0 mmol/ml mean ±S D 25.9±9 0) One month after the onset all patients were in a postinitial remission with no glucosuria found in three daily samples of single voided urine tested with the Clinitest 2-drops-method. Their insulin dose varied between 0 08–0 79 IE/kg body weight (0.39±0.24) At this time the fasting C-peptide levels (Fig. 3) were about the same as those the beta cells produced under maximal stimulation at the onset, indicating an improved beta cell function. Three months after the onset, one patient was no longer in a postinitial remission period which could have been predicted from the low C peptide values both at onset and 1 month later In the remainder of the patients fasting serum C-peptide was almost unchanged that is within the normal range in most of the patients. At this time the beta cell function was further studied by giving a standardized breakfast to 6 patients and measuring C-peptide at certain intervals (15). As shown in Fig. 4 the breakfast was followed by a significant increase in C peptide levels in all the patients tested which means that the beta cells were not exhausted but had a real capacity to answer to the natural stimulation. This was expected as it had been shown by Faber et al. (15) that there is a very good correlation between fasting C-peptide values and the capacity of the beta cells to respond to either glucagon or to a standardized

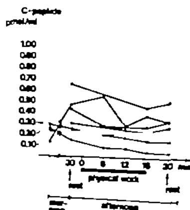


Fig. 5. C-peptide level during rest and physical exercise in 6 children with juvenile diabetes in postinitial remission.

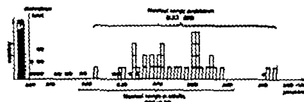


Fig 6. Fasting serum C-peptide in 98 diabetic children in relation to C-peptide in non-diabetic children of the same age.

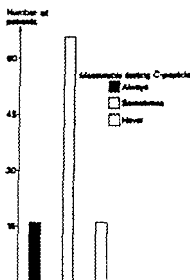


Fig 8 Fasting serum C-peptide in 98 children with juvenile diabetes determined in three serum samples during 1–2 years.

breakfast. Thus in general fasting levels can be used as a measure of beta cell function. The 6 patients above were also studied three months after onset with regard to the possible influence of physical exercise on the C peptide levels (Fig 5) C-peptide was measured at rest in the afternoon about three hours after lunch shortly after a snack, which probably explains the high values During physical work (cycle-ergometry) the C-peptide levels tend to decrease parallel to decreasing blood glucose levels Thus the effect on the physical activity on blood glucose levels does not seem to depend on an increased insulin production

Unfortunately the postinitial remission ends for some unknown reason, and thereafter the beta cells have been considered to have lost

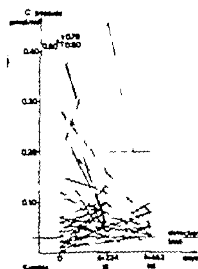


Fig 7 Fluctuations in fasting serum C-peptide in 98 children with juvenile diabetes determined in three blood samples during 1–2 years.

completely their capacity for insulin production However we have measured fasting serum C-peptide in 98 children with juvenile diabetes beyond the postinitial remission. Their age at onset varied between 1–16 years (6.8±3 9) with a duration between 2–17 years (6 7±3 4) We found measurable fasting C peptide in 34 of 98 patients (34 7%) (37) (Fig. 6) In 91 patients C peptide was determined about half a year later (102–364 days 224±51) The number of patients with detectable C peptide had increased to 63 (69 0%) but as shown in Fig. 7 most patients had lower values Another half year later (316–588 days 463±57) 19 of 90 patients had measurable fasting C peptide levels (21 0%) A decrease in some patients would be expected because of the increased duration of the disease but this is *probably not the only explanation for the de*crease in C peptide levels from sample 1 to sample 2 (while there was unchanged or rather *increased values in sample 3)* The decrease in C peptide levels coincides with a significant decrease in insulin antibodies because of the *transition from conventional Lente insulins* to monocomponent insulins in all patients im*mediately after blood sample 1 (36) The most*

attractive hypothesis explaining the decrease in C-peptide values is that the lower levels of insulin antibodies have led to a decrease in the stress on the beta cells and as a consequence lower basal insulin levels (22 25 53) Although there are some fluctuations in C peptide levels between the three occasions it is possible to distinguish one group of 16 patients with measurable C-peptide in all three samples (Fig. 8) and another group including 16 patients who never had any detectable C peptide. The remainder of the 66 patients had measurable C-peptide in 1–2 samples. Together with that we learned about proinsulin in the previous paper these results show that even several years after the postinitial remission period many juvenile diabetics have some persisting beta cell function.

CLINICAL SIGNIFICANCE

Has this beta cell function any effect on the degree of metabolic control? As mentioned above it is reasonable to believe that the beta cell function causes the stable metabolism during the postinitial remission period (12) Binder et al. (5) found a significant correlation between C peptide levels and blood glucose control in adult insulin-dependent diabetics They also found the same positive effect of endogenous insulin secretion on the balance of beta-hydroxy-byturate acid (43) Beischer et al (4) showed that insulin-dependent patients could manage their glucose levels by one daily insulin injection only if they had some residual beta cell function and a preserved stimulatory capacity as measured by C-peptide. Grajwer et al. (21) found measurable CPR in 25 of 35 children with insulin-dependent diabetes The correlation between CPR-levels and degree of metabolic control was significantly positive That the relation to C-peptide really reflects the effect of endogenous insulin production and not the effect of C peptide itself is evident, as there is no metabolic effect of C-peptide either in diabetics or in normal subjects (24).

In our studies of the factors influencing metabolic control in 58 juvenile diabetics with age at onset between 1–13 years (6.0±3 4) and duration of diabetes between 3–14 years (7.3±

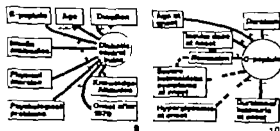


Fig 9 Factors influencing metabolic control in juvenile diabetics

Fig 10 The relation between clinical manifestations and treatment at onset and fasting C-peptide level several years later

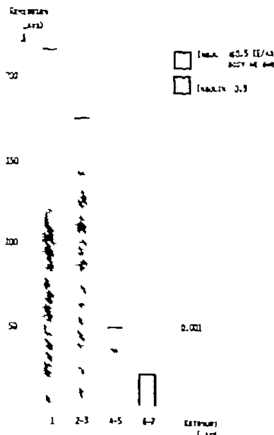


Fig 11 Mean duration of remission in children with juvenile diabetes related to duration of ketonuria at onset.

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(J. L.) Department of Pediatrics
University Hospital
S-581 85 Linköping
Sweden

DISCUSSION

Matts Pehrson. A girl 13 1/2 years old developed diabetes mellitus in August 1976. There was no ketoacidosis at the beginning. At first she was treated only with dietary restriction. In November 1976 her liver function seemed to be impaired and she was sent to a pediatric clinic. Here treatment with insulin (Monotard®) was started at once. A chronic aggressive hepatitis was diagnosed. Treatment with prednisolone was added 1 month after the beginning of the therapy with insulin. The diagram below shows the doses of insulin and the variation of human C-peptide in serum during the first two months of therapy with prednisolone (the determinations of C-peptide were made by Dr Lise Heding, Novo Research Institute, Copenhagen).

Karl Henrik Gustavson. Did you find any statistically significant relationship between insulin requirement and C peptide level during or after the postinitial remission?

Johnny Ludvigsson. Most patients with high levels of C-peptide during remission need low doses of insulin (in most of our cases <0.3 IU/kg body weight). In patients beyond the post-initial remission we have not found any significant relationship between C peptide levels and insulin dose, but we have found a significant positive relationship between C-peptide level and better metabolic control.

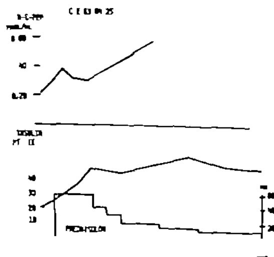
Anders Häger. Please explain the statistical calculations regarding the duration of ketonuria and the C-peptide levels. Is this really evidence for the benefit of the treatment? Couldn't it be explained by the fact that we have various degrees of severity of the disease?

Johnny Ludvigsson. The severity of the disease may certainly play a role in the duration of ketonuria as well as in future beta cell function reflected by the C-peptide level. I believe that an early detection of diabetes is important. However, the relation between ketonuria and C-peptide level is seen also with the blood glucose level on admission and with the severity of ketoacidotic symptoms at onset kept constant in a regression analysis. Further more, we have shown that insulin treatment is important for the duration of ketonuria as well as for the C peptide level later on. These results suggest, but do not prove, that the treatment is of importance not just the severity of the disease.

Bengt Persson. You measured the changes in plasma C-peptide concentrations in juvenile diabetic patients during physical exercise. What was the object of these measurements? How do your results in diabetic subjects compare to those of non-diabetic control subjects?

Johnny Ludvigsson. We were interested in the influence of exercise on the endogenous insulin production in juvenile diabetics to see if this could, in some way, contribute to the explanation of the effect of physical exercise on blood glucose. The results up to now are preliminary and further studies (including non-diabetic control subjects) are needed.

Yngve Larsson. Obviously there is a considerable group of your patients who have very variable levels of C peptide from one time to another. Would you like to speculate on the mechanisms of such variations, whether due to endogenous or exogenous factors?



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(J L.) Department of Pediatrics
University Hospital
S-58185 Linköping
Sweden

THE CLINICAL SIGNIFICANCE OF INSULIN ANTIBODIES

OLE ORTVED ANDERSEN and JØRN EGEBERG

From the Medical Department E, Frederiksberg Hospital, Denmark and the Anatomy Department B University of Copenhagen, Denmark

Treatment of diabetic patients with commonly available insulin preparations results in most cases in the formation of immunoglobulins, which are able to form immune complexes with insulin. They are therefore called insulin antibodies.

The immune complex formation might result in different reactions.

Allergic reactions.
Insulin neutralization.
Vascular damage.

ALLERGIC REACTIONS

Mild transient local reactions have been reported to appear with frequencies from 5 to 50 per cent (6 10 18 20) On the other hand, severe generalized even anaphylactic reactions have been rare. Frequencies from 0 2 to 1 0 per cent have been observed (3 10) Kniker (12) and Dolovitch et al. (8) have shown IgA and especially IgE to be responsible in most cases. Jorpes (11) Yalow & Berson (20) Deckert (4) and Federlin et al (9) found that contaminating impurities in the insulin preparations were responsible for the reactions. During treatment with recrystallized or highly purified insulin preparations allergic reactions have been curiosities

INSULIN NEUTRALIZATION

It is generally accepted that the daily insulin requirement is about 40 units (0.6 units per kg) Insulin requirement of more than 200 units per day is defined as insulin resistance Numerous investigations have established a significantly increased serum insulin binding capacity from insulin resistant diabetics when compared with the binding capacity of serum from non-resistant diabetics Today it is established that insulin antibodies perhaps especial ly IgM (5 7 16) are responsible for the development of most cases of insulin resistance.

In order to elucidate the significance of insulin antibodies for the insulin requirement among non-resistant diabetics, we examined the plasma insulin binding capacity before and several times during treatment with recrystallized NPH-porcine-insulin of non-resistant diabetics (1) Fig. 1 shows the correlation between the plasma insulin binding capacity and the insulin requirement among 43 diabetic patients treated with NPH-porcine-insulin for 9 months. As can be seen we found a significant positive correlation. The results however do not reveal whether the antibodies are of significance for the insulin requirement or individual determined higher insulin requirement causes increased antibody formation

In another investigation (2) some of the patients were treated with highly purified insulin preparations After treatment with NPH porcine-insulin for 6–9 months 75 per cent of patients treated with recrystallized insulin preparations and 15–22 per cent of patients treated with highly purified insulin preparations had formed antibodies (Fig. 2) The content of

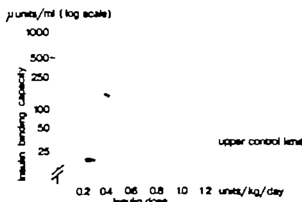


Fig 1 Insulin binding capacity of plasma in relation to the insulin requirement.

Pat.	No.	Age in years	Spearman s correlation coeff. R	P
●	22	7–4	0.4486	$p<0.05$
○	1	25–64	0.1965	$p>0.1$
●+○	43	7–64	0.3946	$p<0.05$

insulin in the recrystallized insulin preparations was 7–13 mmol per mol insulin. The highly purified insulin preparations contained 0.36 mmol proinsulin per mol insulin. The insulin requirement among patients with and without detectable antibodies was compared. After 2 and 5 years of treatment, patients with antibodies had a significantly higher insulin requirement than patients without detectable antibodies. After 2 years of treatment the insulin requirements were 0 61 and 0 42 units per kg per day among patients with and without detectable antibodies After 5 years of treatment the insulin requirements were 0 75 and 0.55 units per kg per day respectively In this investigation most of the patients without detectable antibodies were treated with highly purified insulin preparations and most of the patients with antibodies were treated with recrystallized insulin preparations. The biological effect of the two insulin preparations was equal. Thus the last mentioned investigation indicates that insulin antibodies most likely influence the insulin requirement

Early in the insulin treatment some patients present a decreasing in n need The phenomenon is described as the remission period or the honeymoon. We ha e defined the remission as a continuous reduction in the insulin requirement 2–3 weeks after the beginning of treatment to a dose less than 0.3 units per kg per day for more than two months Relapse was defined as a persistent increased requirement of more than 50 per cent. Among 35 patients fulfilling the criteria for remission 11 patients developed insulin antibodies while 24 patients had no detectable antibodies. Fig. 3 shows the length of the remission period within the first year Patients without detectable antibodies had a significantly longer remission period (Wilcoxon test. $p<0.05$) In animal experiments *Logothetopoulos* (14) among others has demonstrated the neutralizing effect of insulin antibodies on the endogenously produced insulin The present investigation support the assumption that insulin antibodies might neutralize and thereby reduce the supply of endogenous insulin during the remission period

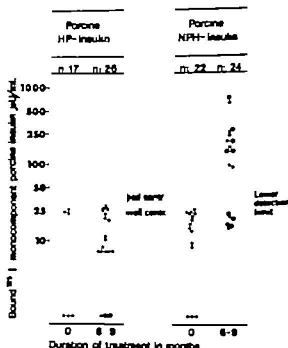


Fig 2 The insulin binding capacity of plasma previous to treatment and after treatment in 6–9 months with highly purified insulin (HP-insulin) and recrystallized insulin (NPH-insulin). The dotted lines indicate the lower limit of detection in poorly and well controlled non-treated patient ○ Examination after treatment for more than 9 months Examination after treatment for 5 months.

VASCULAR DAMAGE

We do not know the pathogenesis of late diabetic complications especially the microangiopathy The complications especially as judged by simple retinopathy occur with the same frequency among patients with insulin dependent juvenile diabetes and patients with maturity onset diabetes not treated with insulin On the other hand severe complications e.g. proliferative retinopathy and nephropathy are significantly more frequent among juvenile diabetics (13 15 17) It is the prevalent opinion that a concurrent pathogenetic factor might be an increased capillary permeability with deposition of plasma proteins on the basement membrane. Insulin antibodies or insulin-anti-insulin immune complexes do not cause the complications, but they might be deteriorating factors.

In an attempt to throw light on the problem we examined the plasma insulin binding capacity of 184 patients with long-term juvenile diabetes. All patients were less than 50 years of age and had onset of diabetes before the age of 20 years. In fig. 4 the columns indicate the mean titres of porcine insulin binding capacity among 110 patients without complications and among 74 patients with complications Even though statistical evaluation did not reveal any significant differences patients with early onset of proliferative retinopathy or nephropathy

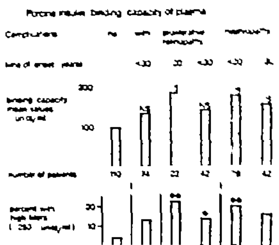


Fig 4 Porcine insulin binding capacity of plasma from juvenile diabetics with and without late diabetic complications. The patients were <50 years of age and had onset of diabetes <20 years of age. Statistical evaluation. Upper part. Wilcoxon test for two samples. Lower part, chi square test. N.S. $p>0.1$ *, $p<0.05$ **, $p<0.01$

showed a somewhat higher mean titre Comparison of the prevalence of high titres revealed that patients with complications especially early onset of proliferative retinopathy or nephropathy had a significantly higher prevalence of high titres than patients without complications. These results are consistent with the concept that insulin antibodies or insulin-anti-insulin immune complexes might contribute to the development of severe complications

Thickening of the endothelial basement membrane has been assumed to be an early morphological change of microangiopathy *Østerby* (21) demonstrated thickening of the glomerular basement membrane in juvenile diabetics after treatment with insulin for 2–3 years.

We have followed the insulin antibody titre measured as the plasma insulin binding capacity in a group of patients during insulin treatment for 8–9 years. In a preliminary study we examined the thickening of the capillary basement membrane from muscles using the method described by *Williamson et al*

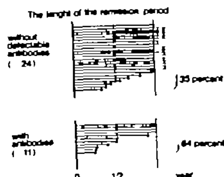


Fig 3 The length of the remission period among patient with and without insulin antibodies. Relapse indicated by star

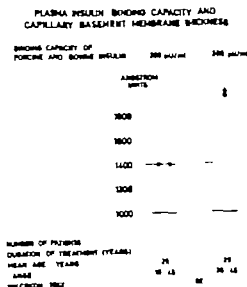


Fig 5 Insulin binding capacity of plasma and capillary basement membrane thickness. Dotted line indicate the 95 per cent borderline for non-diabetic controls, 30–50 years of age.

Fig. 5 shows the thickness of the capillary basement membranes in 7 patients with small or undetectable amounts of antibodies and in 6 patients with high antibody titres. The two groups were comparable as to duration of treatment age and sex. As can be seen the thickness of the basement membrane was significantly greater among patients with high antibody titres

CONCLUSION

Insulin antibodies rarely cause allergic reactions

Insulin antibodies are responsible for the development of most cases of insulin resistance Moreover insulin antibodies seem to be of significance for the insulin requirement among non-resistant diabetics The results presented are in agreement with the assumption that insulin antibodies due to the neutralizing effect on endogenously produced insulin may shorten the remission period

Finally it cannot be excluded that insulin antibodies might contribute to the development of severe vascular complications

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(O. O. A.) Medical Department E
Frederiksbergs Hospital
Denmark

DISCUSSION

Johnny Ludvigsson. In our studies on factors influencing metabolic control in juvenile diabetics we found a significantly negative relation between the level of insulin antibodies and the degree of metabolic control, based on daily control of glucosuria, in contrast to the results of Dixon et al. (*Lancet I* 343 1977) We also found a negative relation between the level of insulin antibodies and C-peptide level beyond the remission, which is in accordance with your negative relation between insulin antibodies and remission. Perhaps the negative effect of insulin antibodies on metabolic control and on endogenous insulin production may explain to some extent the relation between insulin antibodies and vascular complications.

Lise Heding It was interesting to see your demonstration of lower insulin requirements in patients without antibodies. However it is very difficult to explain this observation. The antibodies lead to an increased level of total insulin which has no biological activity and has a half-life of about 1 day The maintenance of these circulating insulin antibodies will lead to an increased dose requirement. On the other hand, the concentration of the bound insulin is normally low and hence this could hardly lead to a significant increase of the insulin requirement. Another possibility is that the antibodies enhance the exhaustion of the beta cell, which then leads to an increased requirement of insulin.

Stefan Aronson. Have you observed an altered insulin requirement when switching from conventional to monocomponent insulin? We have observed a decrease of insulin in all but one of 13 patients studied. The patients switched from Rapitard to Semi-Lente and some of the decrease could be due in part to a concomitant change of species from bovine to porcine insulin. Immunological mechanisms could also come into play as antibody titres fell on the average 40%

Ole Ortved-Andersen. We have not examined for changes in the insulin requirement or insulin-antibody titres in patients switching from one insulin preparation to another Most investigations on the subject have been done in small groups of patients changing species and purity of the insulin preparations simultaneously Folling and Dominiczak in 1975 reported the results from 63 patients switching to highly purified insulin preparations without changing species They did not observe alterations in the antibody titres or in the insulin requirements

Yngve Larsson. We have studied the effect of transition from conventional to monocomponent insulin in more than 90 patients with juvenile diabetes beyond the remission period. The insulin antibody levels were high in most patients before transition and had decreased significantly during the first 6 months after the change but not thereafter There was a very marked difference between patients both with regard to pre-transition antibody levels and post-transition change of these levels. This individual variation is an interesting feature that requires further study We did not observe any significant change in insulin dosage This is in contrast to the findings of among others, Aronsson. However in his material there were one or two cases with extremely high insulin doses before transition, which caused a high mean pre-transition dose. After

exclusion of such exceptional cases the de crease of insulin requirement, in Aronson's material was only minimal

Øystein Aagenaes Hearing that both Yngve Larsson in Linköping and Dr Aronson in Lund have changed all their diabetic children from Rapitard or Lente insulin I would like to know (from Dr Schlichtkrull) if Novo has given a general recommendation to change all patients on "old" insulins to new monocomponent insulins?

Jørgen Schlichtkrull No

Sven Erik Fagerberg The Örebro Clinic has reported in Läkartidningen a study on transition from conventional to monocomponent insulins Our results are in accordance with those described by Yngve Larsson Thus we found no decrease in insulin dose

Goran Blohmé Insulin antibodies were determined according to O Ortved-Andersen every two months for one year in 60 patients treated with conventional insulin for several years Two-thirds of the patients passed from conventional to highly purified porcine insulin We found no change in insulin requirement or degree of metabolic control The level of insulin antibodies remained constant in most of the patients In some of them there was a small decrease while there was a *considerable* increase of insulin antibodies in some other patients.

Ivar Folling We have done a similar study on about 60 diabetics Switching from conventional to highly purified porcine insulin did not influence insulin requirements No major change in antibody levels were seen either although a small decline was found in one group

INSULIN ANTIBODIES IN THE SERUM OF DIABETIC CHILDREN TREATED FROM THE DIAGNOSIS OF THE DISEASE WITH HIGHLY PURIFIED INSULINS

HANS K. ÅKERBLOM and ANNA LIISA MÄKELÄ

From the Department of Pediatrics University of Oulu, Oulu and the Department of Pediatrics University of Turku, Turku Finland

ABSTRACT Fifty-one diabetic children, treated with highly purified, porcine insulins from the diagnosis of the disease were studied for the development of insulin antibodies during the first years of treatment. Sera were obtained before the start of treatment and at repeated intervals thereafter Serum insulin antibodies were measured by three methods in three laboratories. Twenty-nine children were treated with R.I. (rare immunogenic) insulins at one department and 22 with MC (monocomponent) insulins at the other department. Before the start of treatment, serum insulin antibodies were almost invariably zero or below the limit of detection. During the first year a considerable number of cases, more than that reported for adults, formed detectable amounts of antibodies, and more so in the R.I. than in the MC series. The levels were however definitely lower than those observed with the same methods in diabetic children on conventional insulins. Analysis of variance showed no differences between the various age groups. No significant correlation was found between the highest titre of serum insulin antibodies on the one hand and insulin dose or glucosuria on the other hand. The results confirm the concept that children form antibodies to insulin more actively than adults.

KEY WORDS: Diabetic children, highly purified insulins, serum insulin antibodies

In recent years the value of the highly purified pork insulins in the treatment of diabetes mellitus has been assessed in many studies. The number of published studies on adult diabetics is now great, a low or absent immunogenicity being a typical finding. These new insulins have established their role especially in the treatment of insulin lipoatrophy insulin allergy diabetes in pregnancy and the rare instances of insulin resistance (28 8) In contrast to adult diabetics diabetic children have been the subject of only a few published studies. Symonides-Lawecka et al (29) reported a marked rise in serum insulin-binding antibodies in six of 10 diabetic children, treated for 8–16 months with monocomponent insulin from the time of diagnosis of the disease. In three cases the insulin antibody levels rose after viral infection, in two after bacterial infections and in one after treatment with poly vaccine.

Although the definite role of insulin antibodies in the pathogenesis of diabetic microangiopathy is not yet known, there is some evidence to suggest that they might play a part in this disorder (7 30)

Highly purified insulins have therefore recently become the insulins of choice in many countries in the long-term treatment of newly diagnosed diabetic children.

Because children might form a special group among insulin-treated diabetics with respect to possible antibody formation more information was considered desirable on the possible development of insulin antibodies during treatment with highly purified insulins. In order to

exclusion of such exceptional cases the decrease of insulin requirement in Aronson's material, was only minimal

Øystein Aagenaes Hearing that both Yngve Larsson in Linköping and Dr Aronson in Lund have changed all their diabetic children from Rapitard or Lente insulin I would like to know (*from Dr Schlichtkrull*) if Novo has given a general recommendation to change all patients on "old" insulins to new monocomponent insulins?

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The correlation of the results obtained with the various methods was as follows (specimens from 3 weeks onwards):

Methods	No of analyses	Correlation coefficient	*P*
Andersen et al. vs. Christiansen	104	0.71	<0.001
Andersen et al. vs. Welborn et al.	95	0.80	<0.001
Christiansen vs. Welborn et al.	150	0.65	<0.001

Statistical analysis

The Mann-Whitney *U*-test was used for the comparison of the results on insulin antibodies between the R.I and MC series after various lengths of treatment. The possible difference between insulin antibody levels of different age groups was tested by analysis of variance. Student's *t*-test was used for the comparison of the difference between the R.I. and MC series for the mean values of insulin dose and glucosuria after various lengths of treatment. In the analysis of mean glucosuria, logarithmic values were used in the presence of skew distribution of the individual values to the right within group with a normal distribution after logarithmic transformation.

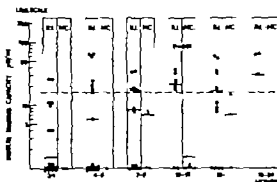


Fig 1 Serum insulin antibodies, measured as insulin binding capacity μU/ml (9) from 3 weeks onwards during the first 2 years of treatment in diabetic children treated from the diagnosis of the disease with highly purified insulins. Type of insulin: R.I.=rare immunogenous (Nordisk Insulinlaboratorium), MC=monocomponent (Novo Industri A/S). The broken line denotes the sensitivity limit of the method. The thick lines within the columns mark the median for the group. The significance of the difference between the R.I and MC groups was tested with the Mann-Whitney *U*-test.

RESULTS

Insulin antibodies

Before the start of insulin treatment the levels of serum insulin antibodies were non-detectable with the following exceptions. Cases VI and VII in the R.I. series had levels around the limit of detection with one of the methods whereas the other methods showed values equal to zero or below the sensitivity limit. After the start of insulin treatment these cases had values below the detection limit with all three methods for a while The third exception was the R.I case XXI whose serum had an ^{125}I-insulin binding value of approximately 10% before insulin treatment, which has subsequently remained at the same level, whereas the values measured with the methods of Andersen et al. and Christiansen were below the limit of detection before treatment and have thereafter repeatedly been zero or below the sensitivity limit.

The first increases of serum insulin antibodies above the limit of detection occurred in some cases of the R.I. series after insulin treatment had lasted 3 weeks or 1 month The values for serum insulin antibodies from 3 weeks onwards during the first 2 years of treatment, measured with the three methods are presented in Figs 1–3 If two specimens were obtained during any period marked by columns in Figs. 1–3 the mean value was taken for the graphic presentation. In some instances the serum sample was not large enough to be divided into aliquots for all three laboratories.

In general a considerable number of the cases particularly in the R.I. series had detectable levels of insulin antibodies in the serum. However the levels were definitely lower than in diabetic children treated with conventional insulins For instance serum insulin antibodies were measured with the same methods and laboratories as in the present study in 44 diabetic children before the change to R.I preparations the range and median values being 2–294 (51) μU/ml by the method of Andersen et al. 0 065–3 900 (1.394) mU/ml by the method of Christiansen, and 5 9–47.3 (22.0) % by the method of Welborn et al. (Mäkelä and Åkerblom unpublished resu s)

In the present study a few di

Table 1 *Age at diagnosis of diabetes mellitus and sex distribution in children treated from the diagnosis of the disease with highly purified insulins*

	Type of insulin	
	R.I.	MC
Boys		
n	15	13
Age at dg., years		
Range	3–15	5–14
Mean	9.7	9.1
Girls		
n	14	9
Age at dg., years		
Range	5–14	6–15
Mean	9.0	9.7

obtain a sufficient number of patients in a reasonable time a collaborative study on insulin antibodies was initiated at two pediatric diabetes clinics in patients treated from the diagnosis of the disease with highly purified insulins. Insulin antibodies have been measured with three methods in three laboratories. The present report is an interim one of a study in progress. It contains data on those children whose duration of treatment exceeds six months.

PATIENTS AND METHODS

Patients

The series consists of 29 diabetic children aged 3–15 treated from the diagnosis of the disease with R.I. insulins[a] (Department of Pediatrics, University of Turku, A. L. Mäkelä) and 22 diabetic children, aged 5–15 years, treated correspondingly with monocomponent (MC) insulins[b] (Department of Pediatrics, University of Oulu, H. K. Åkerblom). Age at diagnosis and sex distribution are shown in Table 1.

The distribution of the patients among the various age groups was similar in the R.I. and MC series. The patients were newly diagnosed diabetics who were admitted to the study consecutively. The duration of treatment as of August 1, 1977 is presented in Table 2.

R.I. = rare immunogenic.

[a] Insulin Neutral Leo® and Insulin Leo Retard® (type NPH). Nordisk Insulinlaboratorium.

[b] MC Actrapid®, MC-Semilente and Monotard® (type lente), Novo Industri A/S.

The aims of the long-term treatment of diabetes mellitus were the same at both diabetes clinics: freedom from symptoms, subjective well-being, normal growth, and avoidance of ketosis and hypoglycemic shock. The insulin regime consisted of short-acting insulin initially for a few days, followed by intermediate-acting insulin or a mixture of short- and intermediate-acting insulins once daily. After the postinitial partial remission several patients were switched over to two injections of insulin daily. For this study the assessment of the balance of diabetes was done on the basis of 24-hour glucosuria results from urine collections done for two consecutive days preceding the visit to the diabetes clinic. Partial remission was defined as the postinitial period of treatment, when the daily insulin dose was at the most 0.5 U/kg, and glucosuria was absent or minimal.

For the analysis of insulin antibodies blood was withdrawn from an antecubital vein before the start of insulin treatment, after 1 to 2 weeks treatment, at discharge and subsequently at each visit to the diabetes clinic at intervals of 1 to 3 months. During hospitalization the specimens were obtained from fasting subjects in the morning, before insulin injection, whereas the outpatient clinic specimens were taken from non-fasting subjects who had received their insulin injection the same morning. The specimens were allowed to clot at room temperature. The serum was separated thereafter by centrifugation, divided in triplicate tubes and stored until analysis at −20°C.

Methods

Insulin antibodies were measured with the methods of: (a) Andersen et al. (9): results are expressed as insulin binding capacity μU/ml (Niels Steensens Hospital, Gentofte). Values exceeding 15 μU/ml are regarded as positive titres. (b) Christiansen (13): results are expressed as IgG binding of insulin, mU/ml (Novo Research Institute, Bagsvaerd). Values exceeding 0.036 mU/ml are regarded as positive titres. (c) Welborn et al. (31) modified, dextran-coated charcoal (18) being used instead of alcohol precipitation to separate free from bound labelled insulin. The final serum dilution was 1:10. Results are expressed as percentage ^{125}I-insulin binding (Department of Pediatrics, University of Oulu, Oulu). Values exceeding 4% are considered as positive titres.

Results on lipemic sera were not considered.

Table 2 *Duration of treatment with R.I. or MC insulins in diabetic children*

Duration of treatment (months)	Number of patients treated with R.I. insulin	MC insulin
7–12	3	7
13–18	6	8
19–24	16	1
25–	4	6
Total	29	22

Table 3 *Mean values and ranges in various age groups of the highest individual titres for patients followed for at least 10–12 months and the results of the analysis of variance between the age groups*

Method	Series		Age group –6 yr	7–11 yr	1 yr	Variance ratio F
Andersen et al. μU/ml	R.I	Mean	39	35	38	
		Range	4–60	0–104	5–66	0.03
			4	8	8	N.S.
	MC	Mean	6		10	
		Range	0–8	(7 15)	5–18	
			3	2	3	
	R.I +MC	Mean	25	30	30	
		Range	0–60	0–104	5–66	0.08
			7	10	11	N.S.
Christiansen, mU/ml	R.I	Mean	0 376	0.611	1.391	
		Range	0.035–0.902	0 004–4.605	0.015–3.879	0.87
			5	9	6	N.S.
	MC	Mean	0 051	0 065	0.058	
		Range	0.031–0.104	0.006–0.124	0 023–0.099	0.07
			3	4	4	N.S.
	R.I.+MC	Mean	0.254	0.443	0.858	
		Range	0.031–0.902	0.004–4.605	0.015–3.879	0.77
			8	13	10	N.S
Walborn et al. % binding	R.I.	Mean	19 8	11 7	19 0	
		Range	7 9–37.2	0.8–35.9	7.5–35.2	1 69
			7	9	10	N.S
	MC	Mean	4 4	6.4	11.2	
		Range	1.5–7.2	1.3–10.9	3.5–24 9	2.26
			4	5	6	N.S.
	R.I +MC	Mean	14.2	9.8	16.1	
		Range	1.5–37.2	0 8–35.9	3.5–35.2	2.15
			11	14	16	N.S.

Analysis of the highest individual titres of serum insulin antibodies in those children who were followed for at least 10–12 months revealed no difference between the "no remission" cases and those with remission (Mann-Whitney U-test)

Three children in the R.I series (cases R.I XV XVI and XVII) and two in the MC series (cases MC V and VI) had a partial remission exceeding 12 months. Three of these patients (cases R.I XV MC V and VI) have never had positive values for insulin antibodies with any of the methods, and the remaining two have had one value each around the limit of detection.

Severe ketoacidosis at admission and insulin antibodies Two children in both the R.I and MC series were admitted in a diabetic precoma or coma (cases R.I IV and IX and MC I and XII) Their insulin antibody titre did not rise earlier than in the other cases nor did their insulin antibody levels differ from those of the other patients.

Clinical aspects

Insulin dose The mean insulin doses ±S D at discharge and 1/2 1 and 1 1/2 year after the end of the partial remission (if any) in the R.I and MC series are given in Table 4 Children receiving R.I insulin had a significantly lower mean dose of insulin at discharge and 1/2 and 1 1/2 year after the end of the partial remission as compared to children on MC insulin.

Table 1 *Age at diagnosis of diabetes mellitus and sex distribution in children treated from the diagnosis of the disease with highly purified insulins*

	Type of insulin	
	R.I	MC
Boys		
n	15	13
Age at dg, years		
Range	3–15	5–14
Mean	9 7	9 1
Girls		
	14	9
Age at dg, years		
Range	5–14	6–15
Mean	9.0	9 7

obtain a sufficient number of patients in a reasonable time a collaborative study on insulin antibodies was initiated at two pediatric diabetes clinics in patients treated from the diagnosis of the disease with highly purified insulins. Insulin antibodies have been measured with three methods in three laboratories The present report is an interim one of a study in progress. It contains data on those children whose duration of treatment exceeds six months.

PATIENTS AND METHODS

atients

The series consists of 29 diabetic children, aged 3–15 years, treated from the diagnosis of the disease with R.I. insulins (Department of Pediatrics, University of Turku, A. L. Mäkelä) and 22 diabetic children, aged 5–15 years, treated correspondingly with monocomponent (MC) insulins (Department of Pediatrics, University of Oulu H. K. Åkerblom) Age at diagnosis and sex distribution are shown in Table 1

The distribution of the patients among the arious age groups was similar in the R I and MC series. The patients were newly diagnosed diabetic who were admitted to the study conse ely The duration of treatment as of August 1 19 pr sented in Table

R.I = rare immunogenic.
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The aims of the long-term treatment of diabetes mellitus were the same at both diabetes clinics, freedom from symptoms, subjective well-being, normal growth, and avoidance of ketosis and hypoglycemic shock. The insulin regime consisted of short-acting insulin initially for a few days, followed by intermediate-acting insulin or a mixture of short- and intermediate-acting insulins once daily After the postinitial partial remission several patients were switched over to two injections of insulin daily For this study the assessment of the balance of diabetes was done on the basis of 4-hour glucosuria results from urine collections done for two consecuti e days preceding the visit to the diabetes clinic. Partial remission was defined as the postinitial period of treatment, when the daily insulin dose was at the most 0.5 U/kg, and glucosuria was absent or minimal.

For the analysis of insulin antibodies blood was withdrawn from an antecubital vein before the start of insulin treatment, after 1 to 2 weeks treatment, at discharge and subsequently at each visit to the diabetes clinic at intervals of 1 to 3 months. During hospitalization the specimens were obtained from fasting subjects in the morning, before insulin injection, whereas the outpatient clinic specimens were taken from non-fasting subjects, who had received their insulin injection the same morning. The specimens were allowed to clot at room temperature. The serum was separated thereafter by centrifugation, divided in triplicate tubes and stored until analysis at −20°C.

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			3	4	4	N.S.
	R.I.+MC	Mean	0.254	0.443	0.858	
		Range	0.031–0.902	0.004–4 605	0.015–3.879	0.77
			8	13	10	N.S
Welborn et al. % binding	R.I.	Mean	19.8	11 7	19 0	
		Range	7.9–37.2	0.8–35 9	7.5–35.2	1 69
			7	9	10	N.S
	MC	Mean	4 4	6.4	11.2	
		Range	1.5–7.2	1.3–10.9	3.5–24.9	2.26
			4	5	6	N.S.
	R.I.+MC	Mean	14.2	9.8	16.1	
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Clinical aspects

Insulin dose The mean insulin doses ±S.D at discharge and 1/2, 1 and 1 1/2 year after the end of the partial remission (if any) in the R.I and MC series are given in Table 4 Children receiving R.I insulin had a significantly lower mean dose of insulin at discharge, and 1/2 and 1 1/2 year after the end of the partial remission as compared to children on MC insulin.

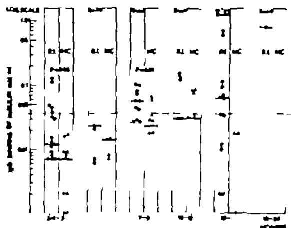


Fig 2. Serum insulin antibodies, measured as IgG binding of insulin, mU/ml (13) from 3 weeks onwards during the first 2 years of treatment in diabetic children treated from the diagnosis of the disease with highly purified insulins. Type of insulin: R.I.=rare immunogenum (Nordisk Insulinlaboratorium) MC=monocomponent (Novo Industri A/S). The broken line denotes the sensitivity limit of the method. The thick lines within the columns mark the median for the group. The significance of the difference between the R.I. and MC groups was tested with the Mann-Whitney *U*-test.

of the R I series had positive titres between 3 weeks and 3 months with one or more of the methods. From the fourth month onward positive titres were also found in the MC series. The values were significantly higher in the R.I series than in the MC series at 10 to 12 months according to the method of Andersen et al. (Fig 1) at 3 weeks to 3 months and at 7 to 9 according to Christiansen's method (Fig. 2) and at all periods between 3 weeks and ? years according to the method of Welborn et al (Fig. 3)

Among those diabetics who were followed for at least 12 months about one half had their highest titre during the first 9 months and the other half between 10 and 12 months Among those patients whose serum insulin antibodies have been followed for more than 2 years some had their highest titre during the first and some during the second year of treatment.

Five children in the R I series (cases R I II III IX XIX and XXIV) developed high levels of insulin antibodies exceeding 1 0 mU/ml as measured by Christiansen's method (Fig. 2) In two cases the titres rose to high levels during the first and in three cases during the second year of treatment.

Among those whose follow-up exceeds 1? months two children in the R.I series (cases R.I VIII and XV) and four in the MC series (cases MC II IV V and VI) have never had detectable amounts of insulin antibodies with any of the methods used the longest observation period being 26-30 months for three children in the MC series

Insulin antibodies in the various age groups The mean values and ranges of the highest individual titres for those patients who were followed for at least 10–12 months are shown in Table 3 grouped according to the age of the patients at the start of the treatment Analysis of variance showed no differences between the various age groups

Partial remission and insulin antibodies Ten of 29 children in the R.I series and seven of 22 in the MC series had no remission whatsoever In the remaining cases the duration ranged from 1 to 18 months in the R I series and from 1 to 13 months in the MC series

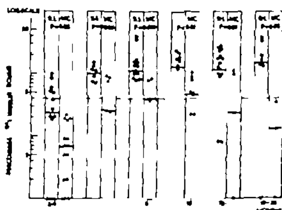


Fig 3 Serum insulin antibodies, measured as percentage ¹²⁵I-insulin bound (31) from 3 weeks onward during the first years of treatment in diabetic children treated from the diagnosis of the disease with highly purified insulins. Type of insulin. R.I rare immunogenum (Nordisk Insulinlaboratorium), MC monocomponent (Novo Industri A/S) The broken line denotes the sensitivity limit of the method The thick lines within the column mark the median for the group The significance of the difference between the R I and MC groups was tested with the Mann-Whitney *U*-test

With regard to possible differences in the treatment, two differences appeared during analysis of the clinical data the significantly lower insulin dose and a significantly higher glucosuria at about the same times in the R.I as compared to the MC series. These differences are naturally interrelated, and we cannot ascribe any role to insulin antibodies in causing poorer balance of diabetes in the R.I as compared to MC insulin treated children. In addition, we found no correlations between the highest titres of insulin antibodies and glucosuria in either series One additional reason for the difference in the balance of diabetes between the R.I and MC series was the difference in the use of two daily doses of insulin. one year after the end of the partial remission five of 22 children in the R.I series and six of seven in the MC series were on two doses and this insulin policy has been clearly proven to improve the balance of diabetes compared to the treatment with one injection daily (2) Furthermore Andersen (5) in comparing younger to older diabetics showed that poor regulation of diabetes was not responsible for a greater antibody formation.

An answer to the question whether the two types of insulins studied differ in their ability to contribute to a good balance of diabetes may be difficult to obtain, particularly in children whose diabetic control is influenced by so many factors. We might get some answer from the extension of this study after having changed some patients to the opposite type of insulin and observing the balance of diabetes in a given period before and after the change the patients serving as their own controls.

Several recent studies (11 ?4 26) indicate that the degree of antibody production may be genetically determined and associated with certain histocompatibility genes The frequency of HLA BW15 was increased among "high responders" in antibody production to insulin in the studies of Bertrams et al (11) and Ludvigsson et al. (-4) whereas Devlin and Parameswaran (16) did not find { frequencies for this antigen between responders and non-responders. We have not yet systematically investigated the HLA types of the subjects included in this study to answer the question about possible differences in, for example HLA BW15 frequencies However in the normal population the HLA BW15-antigen frequency is the same in South Finland, 17.5% and in the region of Oulu (600 km north of Helsinki and northeast of Turku) 19 8% (20) In connection with a study on HLA-types and insulin responses to glucose among siblings 24 diabetic children of the diabetes clinic at the Department of Pediatrics, University of Oulu were typed for HLA (some of them included in the present study) and nine had HLA BW15 (3) In another study ten of 20 diabetic children from southern Finland had HLA BW15 (21)

Infections may stimulate the formation of insulin antibodies (14) although not invariably (5 12) To our knowledge the general infection situation has not been different in recent years in the areas where the R.I as compared to the MC insulin treated children live nor have we found in any particular case relationship between infections in the case history and the development of insulin antibodies Vaccinations may cause a rise in insulin antibodies (29) in some diabetics. In the present study most of the subjects are of school age in which vaccinations are infrequent and the schedule is the same throughout the country

The continuation of the study will hopefully give more possibilities of evaluating the benefits of highly purified porcine insulins and the role of insulin antibodies for the course of diabetes in children. Although our results so far show that insulins of even high purity are to some degree immunogenic for some diabetic children, the highly purified porcine insulins can still be considered as the best available ones.

ACKNOWLEDGEMENTS

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tween the various methods was highly significant. Thus the main trends of the results as regards the titres can be considered indisputable. The foremost result of this study on 51 diabetic children *is that a great proportion of* diabetic children form insulin antibodies during the first years of treatment even if the insulins used are of high purity. However the levels observed were definitely lower than in diabetic children maintained on conventional insulins. Our results thus corroborate the concept that children form antibodies to insulin more actively than adults.

As to the speed of the individual development of insulin antibodies those subjects with detectable levels had their highest titres after different lengths of treatment. Our observation of the highest titre in some cases during the second year of treatment is somewhat surprising, as the highest titre with highly purified insulins has usually been recorded during the first year. In addition in diabetic children on porcine insulin a fall in mean binding of insulin has been described from the second year of treatment on (25). However even in our study among those who were followed for 1 year one half had their peak value of serum insulin antibodies within the first 9 months. The analysis of the highest titres in various age groups did not show differences between the age groups (Table 3).

We could not find a relationship between the partial remission and development of insulin antibodies when patients with and without remission were compared. On the other hand the occurrence of both a long remission and the absence of insulin antibody formation in some patients might indicate that they are causally related. the small dose of insulin needed by these patients might be too weak a stimulus for antibody formation.

A relation between the insulin dose and level of insulin antibodies has been found in many studies (see 5) but we found no significant correlations between these two parameters. Several studies have failed to show a negative correlation between insulin antibodies and the balance of diabetes. According to Kurtz et al (22) it seems possible to maintain the control of diabetes with even very low plasma concentrations of free insulin and the decisive matter at the cell level is the dissociation rate of antibody bound insulin and the association rate of insulin and receptors. Ludvigsson and coworkers (23) however found the above mentioned negative correlation in a thorough analysis of 58 diabetic children who had a duration of diabetes ranging from 3 to 14 years and who were treated with conventional insulins. The finding is one more reason for attempting to minimize the development of insulin antibodies in the long-term treatment of growth-onset diabetes. Our study showed no correlation between insulin antibodies and glucosuria during the first year of treatment.

The "high responder" mentioned in "Results special clinical features" who has suffered from severe hypoglycemic shocks raises the question whether her high levels of serum insulin antibodies are causally related to the hypoglycemic episodes. Harwood (17) described an insulin-treated diabetic with severe hypoglycemic attacks due to slow release of bound insulin. The patient's serum globulins had an unusually high insulin-binding capacity and an unusually slow rate of dissociation of the insulin-antibody complex.

The second main finding of this study is the *evident difference in the levels of serum in*sulin antibodies between the R.I and MC series (Figs. 1–3). The levels rose in the R I series somewhat earlier than in the MC series and when grouped according to the duration of treatment significant differences were found between the two patient series with one of the methods at all time periods between 3 weeks and 2 years. The reasons for these differences may be in the treatment, the populations or in the insulins. We are aware of the limitations in the comparison of two series of diabetic children treated at two different departments and studied with regard to two insulin preparations without randomization within one department.

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(H. K. Å.) Department of Pediatrics
University of Oulu
SF-90220 Oulu 22
Finland

DISCUSSION

Ole Ortved Andersen The two groups of patients treated are living in different places in Finland. Are there any ethnic differences between them?

Hans Åkerblom. No

Hospital for co-operation in the analysis of serum insulin antibodies, Mrs Birgitta Therman, Nordisk Insulinlaboratorium and Mr Teppo Vapaavalta, Novo Industri for shipping of the specimens, Mr Heinz Christophbeink for technical assistance and Professor Kauko Kouvalainen for criticism of the manuscript. We acknowledge the gift of ^{125}I-insulin by Novo Research Institute for determination of insulin antibodies and the support given by the Sigrid Jusélius Foundation (H. K. Å.).

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THE USE OF INSULIN IN THE TREATMENT OF JUVENILE ONSET DIABETES

General Principles

Y LARSSON

From the Department of Pediatrics Uni ersity H spital Linköping S eden

ABSTRACT Insulin is a major tool in the treatment of juvenile onset diabetes in spite of the impossibility of giving it in a physiological way Dosage must be individualized ith the help of mixing short and longacting types of non-immunogenic insulin preparations. Procedures ary with the stage of the disease whether at the onset of diabetes, during the remission period or thereafter Rapid normalization of blood and urine sugar is recommended in the first stage which may partly preserve beta cell function. After the first two years of diabetes practically all patients require insulin twice daily T achie satisfactory metabolic control in diabetic teenagers is difficult and requires an experienced team of paediatricians, nurses, dietitians, psychologists and teachers, as well as informed motivated and cooperative patients.

Insulin has been available for more than 50 years—yet it has not been possible to formulate generally accepted rules for its use in diabetic patients In contrast to the case with several other types of hormonal substitution therapy it has been said—with some exaggeration—about insulin that "it is given in the wrong quantity at the wrong time and in the wrong site" (7) The reasons for this are of course the difficulty or even the impossibility of imitating with exogenous insulin the normal secretory physiology of this peptide hormone the production of which in the pancreatic islet cells is characterized by a very rapid release followed by a very short half life Furthermore the secretion of insulin is dependent on a number of other factors such as food intake the "enteroinsular axis" physical activity and on other hormones affecting the blood sugar homeostasis including adrenaline glucagon somatostatin steroids and thers Of importance also is the fact that insulin i secreted into the portal system passing the liver before it reaches its target organs while exogenously injected insulin goes directly into the systemic circulation Even under ideal conditions it is obviously impossible in cases of insulin deficiency to restore these complicated mechanisms through subcutaneously injected insulin whether once or twice daily

Nevertheless in juvenile onset diabetes exogenous insulin is a life saving therapeutic tool the defects of which cannot justify any kind of nihilistic attitude The tool must be used to the best of one s ability based on scientific principles and practical experience

There are three basic facts that the physician prescribing insulin for diabetic patients should remember (*a*) that insulin is only one piece in the therapeutic puzzle of diabetes (*b*) that its effects are markedly determined to a large extent by the events that take place after injection including rate of absorption, duration of action inactivation, binding to antibodies and possibly also release from antibody complexes and (*c*) that the dosage must

be individually adapted from day to day and thus characterized by a high degree of flexibility

A large number of insulin preparations are available on the market. In Scandinavia, however the offer is limited to the products of only 2 or 3 manufacturers. The quality of these is very high and the paediatrician s choice will depend to a great extent on personal taste and practice. Three requirements should be fulfilled in this choice.

1 With regard to the time action of the insulin preparations three varieties are needed short-acting (duration 0–5 hours) intermediate acting (duration 2–12 hours) and long-acting (duration 4–24 hours)

2 The preparations should be miscible without a change of their individual time action characteristics.

3 They should not cause the formation of insulin antibodies, i.e they should be of the single peak monocomponent or "rare immunogenic" type

These requirements are met by the Novo preparations Actrapid, Semilente and Monotard and by the Neutral and NPH insulins of the Nordic Insulin Laboratory

The goals of insulin treatment are identical with those of diabetes therapy in general which in principle means the restoration of normal conditions, as far as possible. This implies

1 normoglycemia, and the absence of both glycosuria and ketonuria,

2. freedom from the symptoms and signs of diabetes

3 normal growth development and adaptation to life and

4 absence of complications.

These goals cannot be attained however in more than a minority perhaps 10–20% of all juvenile diabetics. I believe, nevertheless, that one should adhere to these goals for the benefit of the few successful cases and as a stimulus for the others. This means that one must be ready to accept the frequent frustrations which occur in those cases in whom particularly during puberty and adolescence, ideal metabolic control seems almost impossible.

More detailed criteria for metabolic control in juvenile diabetes have been published, in Sweden among others by a special commission for diabetes (Socialstyrelsens vårdprogramkommitté) (4) They may be summarized as follows.

General condition good
No symptoms of diabetes
No or minimal symptoms of hypoglycemia during a normal and regular way of life
Height for age and weight for height within normal limits that is within 2 standard deviations of the mean
Puberty normal
Normal physical fitness
Achievements at school satisfactory
Social adaptation non-problematic
Glycosuria control at home –3 times daily the results being entered in a diary Of these tests >65% should contain <1% glucose
Hospital control at least 4 times a year
24 hr glycosuria <200 mmol (36 g)
Fasting blood sugar <10 mmol/l (180 mg%)
Absence of ketonuria
No proteinuria.

The principles of insulin treatment which are used in our department at present may be described with reference to the different stages that are characteristic for the disease:

1 *At onset of diabetes* when the diagnosis is made. This means that one is dealing with a hospitalized but alert child with a typical history pronounced hyperglycemia and glycosuria with or without ketonuria. Two alternative types of treatment may then be considered with regard to the speed with which normalization takes place:

(*a*) Normalization of blood and urine *within 24 hours* This requires treatment with relatively large amounts of insulin and consequently very careful supervision of the patient. Only short acting insulin is used during this period and given subcutaneously in repeated

Table 1 *Approximate size of insulin dose at onset (to be given within the first two hours)*

Age (y)	Ketosis present	No or minimal ketosis
1 2	20 IU	1 IU
3- 5	30 IU	20 IU
6- 8	40 IU	28 IU
9-11	60 IU	40 IU
12 15	80 IU	52 IU

doses In cases with massive ketonuria an initial dosage of 1.5–2 0 units per kg body weight is recommended while in patients with no or minimal ketonuria we give a dose of about 1 0 unit per kg In practice this corresponds to the average doses for the different age groups as shown in Table 1 The recommended first dose of insulin may be divided in two to be given within the first two hours The subsequent insulin administration will depend on the blood sugar reaction to the first dose which may vary a great deal from patient to patient.

(*b*) Gradual normalization *without a set time limit* Insulin is given in low dosage 0.5 units per kg body weight or less and a gradual increase of the dose is prescribed until normal levels of blood glucose are attained This may take two weeks or more

I would definitely recommend the first and rapid alternative which has been used successfully for many years and particularly because of the correlations that have been dem- ... between such treatment the subse ... occurrence of postinitial remission and preserved endogenous insulin production (5)

2. *In the immediate postinitial phase* After the intensive treatment during the first 24 hours transition to a long-acting type of insulin (Monotard or NPH) is recommended and the patient may be treated with such insulin given once daily as early as two or three days after admission Teenagers may possibly constitute an exception as insulin twice daily may be indicated in some cases already in this stage

3 *In the remission period* This stage is characterized by a certain amount of endogenous insulin production a stable metabolism and a daily requirement of exogenous insulin which is usually less than about 0.3 units per kg body weight. In the most obvious cases two or four units a day or every second day may be enough Only in very exceptional cases is it advisable however to discontinue insulin treatment altogether In such cases the character of the disease may be described as subclinical latent or asymptomatic diabetes.

4 *Beyond the remission period* In this stage the duration of diabetes usually is more than two years This is the time when one can expect the really great problems in the treatment of juvenile diabetes. The variations in insulin need are considerable both between patients and within the individual patient from time to time The average dose is about 0.8–1 0 units per kg body weight and 24-hr period. However very often the prescription of insulin is no more than an "educated guess" arrived at through continuous trial and error The problems tend to culminate during puberty and adolescence in connection with the type of total diabetes that also is designated brittle diabetes

These cases represent a challenge that should be answered Even if hospitalization is required now and then, it is in the patients normal environment at home in school and at work that the therapeutic efforts should be made The effect of the treatment and the degree of metabolic control should be assessed primarily on the basis of the patients own day-to-day registration of problems symptoms and signs and particularly their glycosuria tests (Clinitest method) Tests made in connection with the visits to the hospital obviously give information only of the accidental situation not necessarily representative oc curring when the tests were ma ... Since June 1977 kits used for testing the ... and ketone bodies are given ... Sweden to all patients w ...

Two rules apply to ... betics in this stage

Table 2. *Multiple insulin therapy—examples of approximate proportions of dosage*

MT = Monotard insulin (Novo) NPH = NPH insulin (Leo)
AR = Actrapid insulin (Novo), NI = Neutral insulin (Leo)
SL = Semilente insulin (Novo)

Morning			
Long-acting (MT or NPH)	Short-acting or intermediate (AR, NI or SL)	Afternoon Long-acting (MT or NPH)	Total
3 (60)	1 (20)	1 (20)	5 (100)
2 (50)	1 (25)	1 (25)	4 (100)
4 (44)	2 (22)	3 (33)	9 (100)

(*a*) Their blood sugar level tends to be rather high in the morning hours due to the carbohydrate intake at breakfast and the absence of physical activity in the school during these hours Hence, *addition of short-acting insulin* to the early morning insulin injection is almost always necessary In some patients the rise in blood sugar appears somewhat later and in such cases addition of an intermediate acting insulin (e.g. Semilente) might be better When using two types of insulin simultaneously different injection techniques may be used. We recommend that the patients use two syringes but inject through one needle only This gives the best guarantee for an exact dosage without bothering the child with more than one puncture.

(*b*) By giving insulin only once a day it is almost impossible to achieve adequate metabolic control in this stage. To simulate physiological conditions insulin would have to be given before each meal i.e. at least three times daily Such models have actually been recommended and tested in Sweden by Möllerström in the thirties and later by Åkerblom et al. Tchobroutsky et al Jackson et al. and others (1 3 8) A positive correlation between multiple insulin therapy and delayed appearance of angiopathy has also been demonstrated.

Hence insulin should be given *twice daily* in this stage of juvenile diabetes a procedure which is almost always practically and socially feasible. One may discuss when one should start this programme immediately after the end of the remission period, irrespective of the degree of control or wait until the one-dose treatment has failed to give a satisfactory 24-hr control. Others may prefer to postpone the two-dose treatment until the patient has reached puberty Perhaps the decision should be based on an assessment of the endogenous insulin production through the determination of the C-peptide level before and after some type of tolerance test. There are also psychological problems that should be considered when changing the therapy In particular it is necessary that the patients and their families are prepared and motivated for the procedure and accept the minor inconveniences involved.

In multiple insulin therapy the proportion between the individual insulin components varies from case to case. Usually however the evening dose is about 1/3 to 1/4 of the morning dose and within the latter about 1/3 to 1/2 should be short or intermediate-acting insulin (Table 2)

5 *During intercurrent problems* There are many such problems and space does not allow a complete description. Acute *infections* occur as in non-diabetic children. As a rule the insulin requirements increase in these situations The risk of keto-acidosis is particularly great in acute gastroenteritis If the patient is febrile an increase of the insulin dose of about 25% is not unusual but individually based recommendations are necessary Similarly in connection with *surgery* most patients require an increase in insulin dosage In major surgery we recommend half the usual 24 hr dose as short-acting insulin given in the morning, and repeated injections of short-acting insulin postoperatively according to need parallel with intravenous glucose administration. In minor surgery 50% of the usual insulin dose may be given as short-acting insulin and 50% in the form of the patient s usual long-acting insulin preparation.

In connection with increased *phy ical activity* such as in sports contests we

TREATMENT OF DIABETIC COMA IN CHILDREN

HANS K. ÅKERBLOM

From the Department of Pediatrics University of Oulu Oulu Finland

ABSTRACT A short review is given on current aspects of the low-dose insulin therapy of diabetic ketoacidosis, and briefly on the other aspects of the treatment. Frequent intramuscular administration of low doses of regular insulin leads to plasma insulin concentrations, sufficient for maximal insulin biologic activity The intravenous and subcutaneous routes of insulin administration are suitable as well in the low-dose insulin therapy The author described results from a retrospective study comparing the efficacy of large and small insulin doses in the treatment of diabetic precoma and coma in children (1). The i.m. administration of insulin, 0.5 U/kg initially followed by 0.25 U/kg at intervals of 1/2–2 hours led to as rapid disappearance of the signs and symptoms of ketoacidosis as with previously used larger insulin doses. The tendency to hypoglycemia and hypokalemia was milder with the smaller insulin dose. With such modified low-dose insulin therapy it is essential to initiate i.v. glucose administration rather early The responsiveness to insulin may vary from one child to another and infections may increase the need for insulin. Therefore careful individual monitoring of the treatment is important even when using the low-dose insulin therapy

KEY WORDS: Diabetic children, low-dose insulin therapy precoma and coma

Even today the pediatrician must despite steady improvement in the early diagnosis of childhood diabetes mellitus be prepared to cases presenting with severe diabetic i e diabetic precoma or coma. ...k of a delay in the diagnosis and inception of treatment to such an extent that the condition has proceeded to the stage of severe ketoacidosis depends on the abilities of the medical personnel and the care they can render But in addition it depends to a great extent on the level of education and knowledge of the initial symptoms of childhood diabetes in the community at large Young children are especially prone to have an unusually rapid development from the first symptoms to the stage of severe metabolic derangement As recently as 1973 Struwe (1) described a material of 730 newly diagnosed diabetic children of whom 28 (4%) had symptoms for only 1–? days All the cases in the latter group had proceeded to diabetic precoma or coma before the start of treatment. At the Department of Pediatrics University of Oulu which takes care of patients in a northern Finnish province with a large area the Diabetes Clinic comprises 160 patients In the years 1975–76 five new cases of diabetes mellitus were admitted in precoma or coma, three of them having an infection simultaneously Naturally previously diagnosed diabetic children may in some instances especially in the case of severe infection end up in diabetic precoma or coma too

In the following a short review is given on current aspects of the insulin treatment of diabetic ketoacidosis and briefly on the other aspects of treatment as well. The aims in the treatment of diabetic ketoacidosis are:

1 Rehydration restoration of circulation
2 Correction of electrolyte disturbances

3 Smooth" continuous correction of the disturbed metabolism

Insulin is effective and needed for ?) and 3)! Various schemes of insulin administration have been proposed for the treatment of diabetic ketoacidosis the main variations being in the size of the initial dose and the route of administration. Naturally the efficacy and safety of the various schemes are most clearly put to the test in the treatment of the most severe forms of diabetic ketoacidosis pre coma and coma.

LOW DOSE INSULIN THERAPY

Until the early 1970's it was traditional to use rather large doses of insulin. Alberti and associates in 1973 were the first to show that small frequent intramuscular doses of insulin were effective in the treatment of diabetic ketoacidosis (3) Subsequently a great number of reports have been published on this topic, *especially describing the modification of con*tinuous low-dose intravenous insulin infusion. However only a few studies particular ly involving children have appeared comparing large and small insulin doses Frequent i.m. administration of low doses of regular insulin (in adults 5–10 U per hour) produces plasma insulin concentrations of 100 μU/ml (7) sufficient for maximal insulin biologic activity The administration of larger doses (40–50 U per hour) resulted in plasma insulin concentrations of around 1000 μU/ml (7) which exceed the ceiling for maximum biologic activity and are metabolically perhaps not more effective than the smaller doses

Comparative studies

Drop et al. (5) studied 14 diabetics 5 to 15 years old who had 18 episodes of mild to moderate diabetic ketoacidosis. They were allocated randomly to one of two treatment groups and were studied prospectively The administration of 0 1 U of insulin per kilogram of body weight per hour as a continuous i.v infusion was as effective as the initial administration of 0.9 to 1 8 U insulin/kg, one third of it as an i v bolus and the rest subcutaneously followed by 0 1 to 0 25 U/kg s.c every two to six hours. The authors concluded that critically ill ketoacidotic patients may be better treated with the low-dose continuous i v infusion with regard to the absence of delay of effect, and the possibility of late depot effects in dehydrated patients in shock, treated with s.c insulin.

Present study Comparison of large and small insulin dose in the treatment of severe diabetic ketoacidosis in children

Our experience comes from a comparison of "large" and "small" insulin doses in the treat ment of severe diabetic ketoacidosis in children (1) During the years 1969–73 the following scheme was in use. The initial insulin dose was 2–3 U/kg (one half i v one half s.c) and the subsequent doses 0.5 U/kg s c at intervals *of 1–4 hours ("large" dose) Since 1974 the fol*lowing adapted low-dose regimen has been in use: The initial dose was 0.5 U/kg i.m. followed by 0 25 U/kg i.m. at intervals of 1/2–2 hours ("small" dose) the length of the interval depending on the severity of ketoacidosis. The i.v fluid, electrolyte and glucose administration remained the same during both regimens. The patients regained consciousness and the Kussmaul type breathing turned to normal in the same time with both regimens with a significantly smaller insulin dose in the latter regimen (Table 1)

In addition a complete recovery from acidosis occurred in the same time with both regimens and with less insulin in the "small" dose regimen (Table ?). Our experience is that the tendency to hypoglycemia was smaller with the "small" insulin dose as compared to the previously used "large" dose regimen. With the insulin dosage used by us it is essential to *initiate i.v* glucose administration relatively early at the latest during the 3rd–4th hour of therapy We have used 2.5% glucose during

Table 1 *Recovery from considerable or severe ketoacidosis with "large" and "small" insulin dose (7)*

Kussmaul + → −
pH → >7.–

	Insulin dose		
	"large" N=15		"small" N=11
Time hours, mean ±S.E.M.	3.6±0.4	N.S.	3.5±0.4
Insulin dosage, U/kg mean ±S.E.M.	[illegible].5±0.4	$P<0.01$	1.4±0.1

the 3rd–5th hours, 5% during the 6th–7th hour and thereafter 10% glucose. The time of starting i.v. glucose administration and the transfer from weaker to stronger glucose solutions must be monitored individually, and the aim is to keep blood glucose over 11.0 mmol/l until ketoacidosis has disappeared. If the initial blood glucose is at or only slightly above this limit, the administration of glucose has to be started from the beginning of therapy or very shortly thereafter.

Recently even smaller initial i.m. doses of insulin have been reported to be efficient in the treatment of diabetic ketoacidosis in children. Baum et al. (4) used 0.1–0.5 U/kg as the initial dose, and Moseley (10) gave 0.25 U/kg initially followed by 0.1 U/kg every hour until ketoacidosis disappeared and plasma glucose decreased below 11.1 mmol/l. We too have recently changed the repeated dose from 0.25 to 0.2 U/kg. Our present scheme, 0.5 U/kg i.m. initially followed by 0.2 U/kg i.m. at intervals of 1/2–2 hours consists of relatively more insulin than that recommended in the "small" dose regimens for adults. The somewhat larger relative amount of insulin for children may be justified by the fact that infection rather often accompanies diabetic ketoacidosis in children. In addition, the pediatrician does not need to try to find the minimum effective dose of insulin which corrects diabetic ketoacidosis. Inadequate insulin treatment would ensue in some cases because the responsiveness to insulin may vary from one child to another. Warnings have recently been voiced about the possibility of failure in the use of continuous low-dose infusion of insulin (8).

As to the route of administration of insulin during low-dose therapy, Fisher et al. showed recently that the i.v., s.c. or i.m. administrations are equally effective after the first two hours (6). The study showed that an initial bolus of insulin given i.v. (0.33 U/kg) may more quickly establish therapeutic levels that will produce a more rapid fall in plasma glucose and acetone bodies in the early hours of treatment. The authors recommend that therapy be initiated with an i.v. bolus of insulin followed immediately by hourly i.m. insulin doses.

FLUID AND ELECTROLYTE THERAPY

Besides the insulin therapy, attention must also be paid to the other aspects of the treatment of diabetic ketoacidosis. The truly critical factors in the treatment of diabetic ketoacidosis are an adequate fluid and electrolyte replacement and frequent monitoring of the patient (6).

In our study the tendency to hypokalemia was slighter with the "small" as compared to the "large" insulin dose: The mean (±S.E.M.) of the lowest recorded plasma potassium value in the cases presenting in diabetic precoma or coma was 3.3±0.2 mmol/l with "small" dose

Table 2 *Complete recovery from considerable or severe ketoacidosis with "large" and "small" insulin dose (2)*

pH→>7.35

	Insulin dose		
	"large" N=15		"small" N=11
Time hours, mean ±S.E.M.	10.4±1.5	N.S.	10.3±1.6
Insulin dosage, U/kg, mean ±S.E.M.	3.9±0.6	$P<0.05$	[illegible].3±0.2

and 2.9±0.1 mmol/l with the "large" dose, $P<0.05$ (?)

The plasma potassium level decreases rapidly and usually reaches its nadir 1–4 hours after the start of treatment. Therefore the i.v. administration of potassium (30–40 meq/l) should be initiated within the first hours of therapy in cases with a normal or reduced plasma potassium concentration. In hyperkalemic and/or oliguric patients the potassium administration should be started later. Continuous ECG monitoring is essential in the supervision of potassium treatment. Because ketoacidotic patients also have a deficit of inorganic phosphorus and an increased consumption of it, potassium administration is recommended as potassium phosphate.

The use of bicarbonate is debatable. Convincing evidence has been presented that there are several risks associated with bicarbonate administration among them cerebral edema. The present concept is that bicarbonate is rarely, if ever, needed in the treatment of diabetic acidosis (9).

Hyperosmolar diabetic coma may occur in children, too. The syndrome has been described in particular in children with preexisting neurological damage and the mortality is high (11). The risk of rapid changes in osmolality is especially great during the treatment of this form of coma, with the subsequent risk of cerebral edema. In the treatment a very careful gradual administration plan of glucose fluid and electrolytes is needed.

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Department of Pediatrics
University of Oulu
SF-90220 Oulu 22
Finland

DISCUSSION

Bertil Thalme

1. At what pH do you recommend correction of the acidosis with Na-bicarbonate?

2. How much potassium should be added to the intravenous treatment during the first hours?

3. Often 0.9% NaCl is used in the initial rehydration. As the concentrations of sodium and chloride are the same, about 154 mmol/l, this means that an excess of sodium and chloride are given. The excess of chloride could increase a metabolic acidosis. Have you con-

Table 1 *Symptoms of hypoglycemia*

Mainly mental symptoms
anxiety tension
hunger fatigue
irritability aggressiveness
changes in consciousness
Mainly neurologic symptoms
sweating, flushing, pallor
vomiting
vertigo, tremor clumsy movements, ataxia
diplopia, large pupils
seizures

Hypoglycemia of episodic character with minor central nervous system manifestations appears more or less frequently in all children with diabetes. These together with more severe symptoms are divided into mainly mental and mainly neurological ones (Table 1) It is well-known that no strong correlation exists between hypoglycemic symptoms and the blood glucose level. The neurologic picture resulting from abnormal cerebral metabolism secondary to hypoglycemia may depend on the rate of fall of blood glucose the duration and severity of low levels of blood glucose the age at which the hypoglycemia occurs and the existence of a cerebral dysfunction. A posthypoglycemic encephalopathy is very rare.

The most salient of the hypoglycemic symptoms is seizure attacks with unconsciousness. The differential diagnosis with epilepsy may be difficult especially in the presence of epileptogenic patterns in the electroencephalogram. Such patterns can also be seen in normal children selected according to very strict criteria of normality (2, 3 6)

Conceivable criteria for establishing the diagnosis of seizures associated with hypoglycemia are.

1 seizures associated with hypoglycemia occurring spontaneously or induced by fasting,

2. no seizures in the absence of hypoglycemia,

3 disappearance of seizures following the administration of glucose

It must be pointed out that the blood glucose level found on admission to a hospital after a hypoglycemic seizure attack at home is not at all relevant for the glucose level existing during that seizure

MATERIAL

During 1960 through 1973 all children with diabetes mellitus controlled at the Children's Hospital, University of Göteborg, were examined by the author The total material comprised 257 children born between 1947 and 1970. There was no sex difference. A diagnosis of diabetes mellitus had been made from 1951 onwards. Most children finished their pediatric controls at an age of 17 18 years.

The children were exposed to serial electroencephalographic (EEG) examinations the results of which will be reported separately (5). Two children had clinically proven epilepsy—one girl had seizures of grand mal and petit mal type and one boy showed astatic-myoclonic seizures as well as psychomotor seizures. This makes prevalence of 0.8% which is not statistically significantly different from the figure of 0.5% in the metabolically healthy population.

Two studies have been published on subgroups of the original material. The first one was published in 1966 and is a combined clinical and neurophysiological study on 85 children between the ages of 2 and 16 years (4). The second one was published in 1974 and is mainly a psychological study with items correlated to clinical and EEG variables in 59 diabetic schoolchildren aged 7 through 15 years (8). Eleven children attended both studies, though at different ages.

RESULTS

Hypoglycemia and neurologic disturbances manifested mainly as seizures occurred in the first-mentioned material in 22% In the second investigation the corresponding figure was 37% Nerve conduction velocity studies were performed in both series Pathologic conduction velocity was found in the peroneal nerve in 9% in both series the reduced nerve conduction velocity being related to age duration of diabetes and obviously to "poor" diabetic control The study by Fällström in collaboration with the author will be investigated more close as the results will give some evidence to the etiology of the increased tendency to severe hypoglycemic reactions in certain chil-

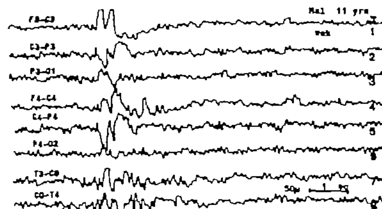


Fig. 1 Episodic low frequency activity with paroxysmal features appearing at rest.

dren. The assessment comprises an intelligence test, a series of projective techniques interviews with the children their parents and teachers, and an EEG investigation (for details see ref. 8)

The EEG findings were compared to findings in the EEG of 500 age-matched normal children selected according to strict criteria of normality (2) The alpha frequency was significantly lower in the diabetic group than in the "controls" The alpha amplitude also was significantly lower in the diabetic children. Non-rhythmic low frequency activity occurred in 38% of the diabetic children and 17% of the controls" a statistically significant difference. In five diabetic children this type of pattern appeared episodically at rest, an occurrence which never could be demonstrated in the "controls" and therefore must be regarded as abnormal (Fig. 1) Paroxysmal activity (mainly epileptogenic) occurred at rest in 2.7% of the controls" and in 11% of the diabetic children (six cases) a significant difference which accounts for a significant difference in total paroxysmal activity (findings during activation with hyperventilation, light sleep and intermittent photic stimulation included) between the two groups. The above-mentioned five children also showed paroxysmal activity at rest and in three cases paroxysmal activity during activations. Although not diagnostic by *itself* the finding of an increased amount of paroxysmal phenomena reinforces the abnormal character of these EEG-records

The neurological symptom of "seizures in connection with hypoglycemia" was subjected to a closer analysis This symptom occurred three times in two children one having a normal EEG twice in six children three having normal EEG's and once in 14 children five having normal EEG's The results of correlation analyses and so-called R factor analysis are shown in Table 2. The aim of the R-factor analysis was to find patterns of interaction between important items revealed by the correlation analyses The five children showing an abnormal EEG clearly present the linkage between EEG-finding and clinical as well as psychological data (Table 3)

Table 2. *Hypoglycemic convulsions*

A. Relevant statistically significant positive correlations between hypoglycemic convulsions and
- age
- perceptual disturbances
- emotional lability
- EEG with paroxysmal activity
- cerebrolesional traits (girls)

B. R-factor analysis

Factor XI
- behaviour disturbances (tics, excessive nailbiting etc.)
- hypoglycemic convulsions
- degree of control

Factor XIII
- EEG with paroxysmal activity
- hypoglycemic convulsions
- duration of disease
- number of hospitalizations

Table 3 *Diabetic children with episodically appearing non-rhythmic low frequency activity*

Relevant electroencephalographic clinical and psychological findings. M = male, F = female + = unequivocal, (+) = equivocal, 1 = add parox act during intermittent photic stimulation, = add parox act during sleep. For further details, see ref 8

			Paroxysmal activity at rest						
Case	Sex	Age	Spikes/ sharp waves	Paroxysmal slow activity	Duration of disease	Degree of control	Hypoglycemic convulsion (no. of attacks)	Paroxysmal abdominal pain/ headache	Tics, nail-biting etc.
7	M	9.02		(+)	6.04	2	2	+	+
11	M	10.10	+	+ 2	6.00		2	+	+
14	M	1..01	+	+	6.03	2	1	+	+
6	F	10.00	(+)	1	3.06	3	3	+	+
31	F	14.00	+	1, 2	7.09	3	1	+	+

DISCUSSION

Like some other authors a relation between hypoglycemic attacks and signs of brain damage and/or EEG abnormalities has been found (1 7 9 10 11 13) Most authors consider repeated hypoglycemic episodes as the primary cause of this "diabetic encephalopathy" while some have suggested the existence of a primary "diabetic encephalopathy" with hypoglycemia as a secondary manifestation (12 14)

In diabetes mellitus the metabolic defect may lead to a permanent cerebral dysfunction with resulting cerebrolesional symptoms and EEG-abnormalities The general occurrence lower alpha frequency and more non-rhythmic low frequency activity in the EEGs of diabetic children compared to controls is indubitably an expression of this The metabolic defect is treated with insulin in order to achieve normoglycemia. In infantile diabetes mellitus this however may be difficult and hypoglycemia of different degrees now and then appears. Repeated episodes of hypoglycemia may cause functional and metabolic disturbances of the neurones but are probably of minor importance as causal factors since diabetic children with no signs of hypoglycemia also have abnormal EEG tracings On the contrary children with hypoglycemic seizures may show a completely normal EEG It is known that genetic factors are important determinants of some abnormal EEG patterns. The metabolic defect in diabetes mellitus has a genetic basis and this is also true for the individual sensitivity to hypoglycemia. Other factors influencing these mechanisms as well as the EEG and mentality are pre- peri and postnatal events age and cerebral maturation. Mental disturbances mainly behaviour disorders, are dependent on the degree of hypoglycemia and also serve as a feedback mechanism to fluctuations of the metabolic state

It is thus obvious that many factors control the disposition to react with neurologic symptoms of hypoglycemia, the main one probably being genetic (Fig. 2) Two children do not have the same sensitivity to hypoglycemia—one child perhaps only reacts with simple symptoms while the other child at the same blood glucose level reacts with loss of consciousness and convulsions

In summary the author supports the theory

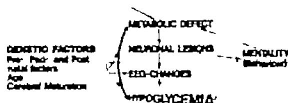


Fig 2 Hypoglycemia and neurological disturbances. The influence of multiple factors.

WISC (sta- ndard)	Maladjust ment index (Bender)	Aggres- sivity (Rorschach)
7	3	+
8	4	+
7	3	+
7	3	+
5	3	+

of a primary "diabetic encephalopathy" with an individual sensitivity to react to hypoglycemia with neurologic symptoms dependent mainly on basic genetic factors.

In the management of the diabetic child it is important to keep the blood glucose at a level that avoids hypoglycemic accidents In cases in whom it is difficult to achieve a stable glucose level with dietary and insulin treatment, resulting in repeated episodes of hypoglycemic seizures the "convulsive threshold" must be raised with anti-convulsant therapy In this context a warning against the use of phenytoins must be presented A chronic use of phenytoin may give rise to polyneuropathy which can superpose the subclinic diabetic polyneuropathy that occurs in about 9% in child diabetic materials (4) Phenytoins are also diabetogenic since they block the insulin release from the beta cells and also reduce insulin synthesis The drug of choice is carbamazepine (Tegretol®)

In several cases it is important to ascertain if the basic cause of the metabolic instability with hypoglycemia and seizures eventually can be epilepsy Then repeated EEG examinations must be performed—sometimes in connection with provocative fasting.

The problem of hypoglycemia and neurologic disturbances deserves further research work before it can be finally solved.

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Department of Pediatrics
University Hospital
S-581 85 Linköping
Sweden

DISCUSSION

Niels Schwart Sorensen You warned against the use of phenytoin which has undesirable effects in many respects I quite agree with you but I should like to emphasize that phenytoin also interacts in a negative way with the metabolism of 25-hydroxy-cholecalciferol.

Orvar Eeg-Olofsson. The phenytoins have many side effects involving several organ systems Especially in children and adolescents the cosmetic side effects constitute a problem. I use carbamazepine as the drug of first choice

Sven-Erik Fagerberg Were there any deviations in EMG or in nerve conduction in those children with pathologic EEG?

Orvar Eeg-Olofsson No such correlations were found (see ref 4)

THE ABSORPTION OF INSULIN

JØRGEN SCHLICHTKRULL

From the Novo Research Institute, Copenhagen, Denmark

ABSTRACT It is desirable to improv metabolic control in diabetics receiving insulin. Studies on insulin kinetics provide information that may be useful in the optimization of the injection scheme. Absorption has been measured using ^{125}I-insulin as marker and counting the residual activity with crystal detector. Plasma insulin has been measured (by radio-immunoassay) in the absence of insulin antibodies. The relationship between the rate of absorption and exogenous hyperinsulinemia was analyzed using simple mathematical model. The time course of plasma insulin was calculated for various insulin preparations, including mixtures. The data suggest the significance of the injection site for the effect of insulin, e.g., more rapid effect after injection into the abdominal subcutaneous tissue. The pattern of exogenous hyperinsulinemia in patients treated with insulin bears no resemblance to that in normal subjects. The calculated patterns of exogenous plasma insulin after injection of arious preparations suggest that insulin therapy might be improved to obtain better and more physiological metabolic control.

KEY WORDS: Insulin therapy, insulin absorption, plasma insulin, injection, insulin antibodies, insulin preparations

In normal subjects continuous β-cell insulin secretion into the portal vein is adjusted via homeostatic mechanisms to maintain glycemia within narrow limits irrespective of whether the subject is fasting exercising or in the post absorptive state after a meal. The diurnal pattern of glycemia and plasma insulin variation is exemplified in Fig. 1

In diabetics with little or no β-cell function, exogenous insulin substitution is necessary to maintain life. Fortunately it is not essential for normalization of the blood sugar that the insulin is supplied via the portal route (4) Good blood sugar control can be obtained by continuously monitoring glycemia and feeding the data into a programmed computer which regulates the delivery rate of a pump that infuses insulin into a vein (1) Implantable devices have been under development for some years to supply insulin at the correct computorized speed derived from a preset program and continuous measurements of gl[...] With the formidable problems encountered, e.g. in keeping the glucose sensor working properly it is unlikely that this method of treatment will be realized and have practical value within the next 10–20 years if ever

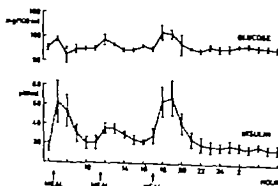


Fig 1 Diurnal variation in blood glucose and plasma insulin based on data published by C. Malherbe et al., Circadian variations of blood sugar and plasma insulin levels in man, *Diabetologia* 5 397 1969 The 4 subjects (group) received three standard meals of different composition at 6:30 a.m., 11.30 and 5.00 p.m.

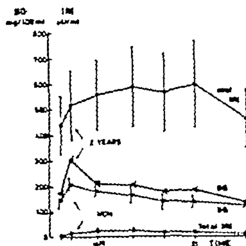


Fig Means and S.E.M. of total immunoreactive insulin and blood glucose in a group of 5 short-term patient (<1 month of insulin treatment) without insulin antibodies and in a group of 19 long-term patients (> years of insulin treatment). Reproduced from S. M. Rasmu sen et al., Serum IRI in insulin-treated diabetics during a 4-hour period, *Diabetologia* 11 151 1975 Reproduced by courtesy of the Editors.

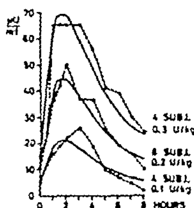


Fig 4 The plasma insulin concentration is calculated as the convolution integral of the function describing the rate of absorption and the exponential function describing the disappearance of insulin from plasma. It was fitted to the data published by Galloway et al., A comparison of acid regular and neutral regular insulin, *Diabet* 22 471 1973 assuming equal rates of absorption in normals and diabetics, a half life of 5.5 min for plasma insulin and a constant (low) level of endogenous insulin. These levels and the volume of distribution were estimated by the least squares curve fitting.

Preplanned insulin infusion without glucose monitoring has been found superior to conventional therapy (5) but is of course not a practical alternative in daily life

One might speculate if the as yet unknown active part of the insulin molecule may be mimicked and given as a pill or if it may be ome possible to regenerate or transplant β-



Fig 3 Absorption of Actrapid from femur after s.c injection. The dots and intervals represent means and S E.M of 33 diabetics, published by C Binder et al (ref 3). The curve fitted by least squar α p (βt) (1−α) exp (−αβt/(α−1)) Its derivat the broken urve) represents the rate of absorption in pe t pe hour of the injected insulin dose.

cells It is however a realistic guess that diabetics will depend on insulin injections for the next 20 years It is a fact that present-day insulin substitution therapy keeps the patient alive but it does so with subjective symptoms and progression of invalidating late manifestations

The probable cause of the shortcomings of insulin therapy is the erratic and unphysiological insulinemia which varies depending on the more or less fortunate injection scheme the actual readiness of the tissue to absorb the injection and the binding to circulating insulin antibodies.

The role of antibodies is exemplified in Fig. 2. The concentration of total extractable plasma insulin amounted to 400–600 $\mu U/ml$ in the long-term patients with plasma insulin antibodies whereas the level was below 50 $\mu U/ml$ in the short-term patients having no insulin antibodies In patients with plasma insulin

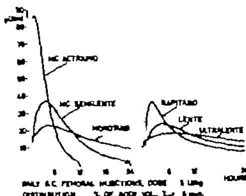


Fig. 5 The rates of absorption are estimated from absorption data as outlined in Fig. 3 and correspond to daily injections given at time zero. The absorption data were obtained by C. Binder and T. Lauritzen, personal communication and published data, ref. 2, and O. K. Faber et al., Insulin Monotard og Insulin Novo Lente® *Ugeskr Laeg* *137* 2510, 1975

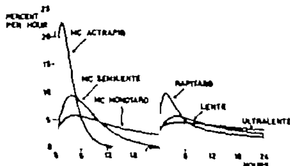


Fig. 7 The plasma insulin concentration curves were calculated as outlined in Fig. 4 using the stated values of insulin dose, $T_{1/2}$, volume of distribution and the rates of absorption shown in Fig. 5.

bound to antibodies it is impossible with the methods now available to determine the level of free active insulin and the effect of an insulin injection becomes even more unforeseeable than in the absence of antibodies.

In the absence of significant insulin antibody binding, the concentration of exogenous plasma insulin is determined by the dynamics of insulin absorption, distribution and disappearance. The course of absorption of an insulin injection can be determined by labelling the insulin with ^{125}I and placing a crystal detector over the site of injection. In this way residual insulin can be measured as its level declines with time, the slope being the rate of absorption. Fig. 3 represents an average of measured residual insulin after injection of fast acting Actrapid® (neutral insulin solution). The rate curve obtained by differentiation shows that it takes almost two hours for the insulin to be absorbed at maximum rate, viz. approximately 25 % of the dose per hour. The absorption data on residual insulin or the rate of absorption have no direct relevance to the problem of metabolic control because the optimal insulin delivery is unknown. Infusion studies may, however, provide this information and make it possible to calculate an optimal injection scheme. Its success will depend on the variations in the patient's need for insulin and on the variation in absorption.

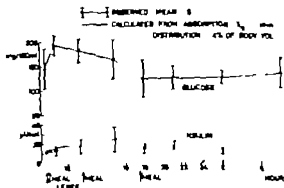


Fig. 6 The observed data have been published by S. M. Rasmussen et al. (The 4 on Lente out of the 5 short-term patients shown in Fig. 2.) The least squares fitted curve was calculated as outlined in Fig. 4, using the stated values of $T_{1/2}$, distribution volume and insulin dose. A constant level of endogenous plasma insulin (about 6 µU/ml) was estimated by least squares.

The absorption may also be characterized by the resulting plasma insulin levels, as shown in Fig. 4 for normal subjects. The dotted lines represent the actual measurements, whereas the solid curves were calculated from Actrapid absorption data on the basis of the following few simple assumptions. 1) Absorption in the normal subjects is the same as in the patients. 2) The insulin absorbed is distributed immediately and u

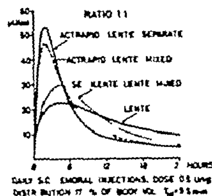


Fig 8. The plasma insulin concentration curves were calculated as outlined in Fig. 4 using the values of insulin dose $T_{1/2}$ volume of distribution and rates of absorption from Fig. 5 and the rates based on absorption data (Actrapid Lente mixture) obtained by T Lauritzen, personal communication.

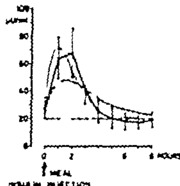


Fig 10. Plasma insulin concentration profiles. The full line with SEMs represents the values in Fig. 1 after the *evening meal. The broken and the dotted curves represent* calculated concentrations based on absorption of Actrapid® from femur and abdomen, respectively ref. 3. In the calculation the dose was 0.16 U/kg, $T_{1/2}$=5.5 min., and the volume of distribution 17.4% of body volume. A *constant level of 20 μU/ml of endogenous plasma insulin* (dot-and-dash line) was assumed.

ly in one pool only estimated at 17.4% of body volume and including the blood plasma. 3) The insulin disappears with a half life of 5½ min. 4) *The low level of endogenous insulin* remains unchanged The assumptions are *rough* but the approximation fits reasonably well with the experimental data.

The simple model was tested with insulin Lente using the absorption data shown in Fig. 5 with the result illustrated in Fig. 6. To obtain the best fit in the calculation, a constant endogenous insulin level of 6 μU/ml was assumed. This is not unreasonable since the *patients were new on insulin*

Since the patients had no insulin antibodies *free and active plasma insulin could be meas*ured by radioimmunoassay The values were not significantly different from the estimates calculated from the model The flat plasma insulin pattern bears little resemblance to the normal pattern (Fig. 1) which has large peaks at 7 a.m and 7 p m and the lack of homeostasis is apparent from the blood sugar (Fig. 6)

Reverting to the model we can depict the time course of absorption in terms of insulinemia, as shown in Fig. 7 Since in the illustration an injection of 35 U/70 kg is given only *once daily at time 0* (e g. at 7 a.m) *the fasting* serum insulin is 0 in the case of Actrapid and Semilente but it is about 10 μU/ml with the other preparations which overlap into the next day

The question of miscibility has been examined with the results shown in Figs 8 and 9

The addition of Actrapid to Lente or Monotard provides a stronger initial effect than the addition of Semilente and it is not much different to that of separate injections

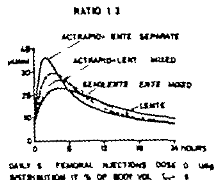


Fig 9 The plasma insulin concentration curves were calculated as outlined in Fig. 4 using the values of insulin dose $T_{1/2}$ volume of distribution and rates of absorption from Fig. 5 and the rates based on absorption data (Actrapid® Lente® mixture) obtained by T Lauritzen personal communication.

Binder et al. showed (3) that the absorption is quicker from the trunk than from a limb as demonstrated for Actrapid in Fig. 10

The plasma insulin after abdominal injection is closest to the normal following a meal (7 p.m. Fig. 1)

In diabetics exercise of a limb injected with insulin has been found to increase the rate of absorption and lower the blood sugar It was suggested that non-exercised injection areas such as abdomen be used to reduce exercise induced hypoglycemia (6)

The timing of absorption of an insulin preparation is not only a question of the injection site and exercise one must also consider the important variation from patient to patient as well as the day-to-day variation within patients (2). The variation is likely to influence the blood sugar for instance when absorption is increased during exercise.

In conclusion

1 Circulating insulin antibodies interfere with the activity of absorbed insulin and invalidate the measurement of insulin activity in plasma.

2. The plasma insulin pattern in insulin treated patients bears no resemblance to that in normal subjects

3 The timing of absorption of an insulin preparation varies unpredictably from patient to patient and from day to day

4 It is suggested that insulin therapy be revised with a view to improving the metabolic control

ACKNOWLEDGEMENT

The mathematical calculations and the curves representing them were made by my colleague An. Volund, M.S., lic. techn., on the basis of data recorded at the H[illegible] Hospital by Dr C. Binder and Mr T Lauritzen.

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Novo Research Institute
Novo Allé
DK 2880 Bagsvaerd
Denmark

DISCUSSION

Anders Häger In the light of Jørgen Schlichtkrull's presentation could the panel give practical recommendations regarding injection sites in children?

Jørgen Schlichtkrull On the basis of the finding of Koivisto et al one would expect to minimize the disturbing effect of exercise on absorption by using the subcutaneous abdominal tissue. At this site absorption is quicker which is likely to be beneficial In m[illegible] this site which is very rarely used, should be tested to see if it can provide better metabolic control.

Øystein Aagenæs We tried to get our patients to use the abdomen as the injection site, but we found relatively large psychological problems with getting the patients to accept [illegible]

Jørgen Schlichtkrull Perhaps [illegible] resistance can be overcome by [illegible]

posable needles and a better injection technique.

Gunnar Meeuwisse The information given by Schlichtkrull is interesting and important but I am partly disappointed after his talk. The title "Insulin absorption" could also mean absorption from the intestine After having heard Falkmer's lecture yesterday one wonders if vertebrates secrete and manage to absorb insulin from the gut why cannot man absorb insulin Is there any research going on in this field?

Jørgen Schlichtkrull Not to my knowledge The results so far obtained with oral administration have been hopeless

Niels Schwartz Sørensen I am aware of earlier attempts to treat diabetes with insulin per orally These experiments were carried out in the fifties The patients were treated with high amounts of insulin mixed with an extract from worms Ascaris lumbricoides containing antitrypsin. It was possible to obtain a significant decrease of blood glucose but the resorption of insulin was very variable. Thus the treatment was without any practical interest. However it is of theoretical interest that insulin can pass the intestinal mucosa with intact biological activity I should like to ask you if you have any experience concerning release of insulin induced by ultra-sound treatment of subcutaneous infiltrations resulting from insulin injections?

Jørgen Schlichtkrull No I have no information on this subject

ASYMPTOMATIC DIABETES IN CHILDHOOD AND ADOLESCENCE

A Review

A. HÄGER

From the Department of Pediatrics, University Hospital, Linköping, Sweden

ABSTRACT An account is given of the present conception of asymptomatic (chemical) diabetes in the pediatric age group, which also has been termed MODY (maturity-onset type of diabetes of young people). Long-term studies show that about 10% will eventually decompensate to overt diabetes. In contrast to chemical juvenile-onset type of diabetes the inheritance of MODY seems to be autosomal dominant in many cases. Some authors have suggested that insulin resistance exists in non-obese patients with asymptomatic diabetes, but this view is not supported by observations of the author. Obese patients should reduce their body fat, but other therapeutic approaches are difficult to evaluate because of the normal fluctuation of the disease. There is no general agreement in the literature concerning the value of insulin treatment. The author supports the view that insulin treatment should be started in the late stages of chemical diabetes just before symptomatic disease emerges. In the long run this approach may ameliorate the condition due to the preservation of some beta-cell function for long periods. An unsettled question is whether early insulin treatment in asymptomatic diabetes will delay diabetic vascular complications.

KEY WORDS: Prediabetic state, asymptomatic diabetes, chemical diabetes

Diabetes in childhood and adolescence usually means a disease with sudden onset and often acute symptoms with ketoacidosis. However since the report by Fajans and Conn in 1960 (4) gradually more attention has been focused on mild forms of diabetes in these age groups sometimes called asymptomatic (chemical) diabetes or maturity onset type diabetes of young people (MODY) (6 7 10 12–17 19). These mild forms of diabetes are not ketosis-prone have no classical symptoms of diabetes but have abnormal glucose tolerance tests and intermittent glucosuria. The oral glucose tolerance test is considered to be superior to the intravenous route in the screening of minor abnormalities in carbohydrate tolerance (16)

NATURAL HISTORY

The natural history of asymptomatic diabetes in children and adolescents is characterized in most cases by a non-progressive course but sometimes amelioration or deterioration of the carbohydrate intolerance may occur in an unpredictable manner Indeed the statement of Fajans must be emphasized. "We should accept that fluctuations in carbohydrate intolerance may be part of the early natural history of the disease" (5) Rosenbloom et al. (16) have compiled data from nine studies of chemical diabetes in children with observation times up to 17 years and have found that about 10% decompensate to overt insulin-requiring diabetes.

ETHIOLOGICAL ASPECTS

1 *Inheritance*

Classical juvenile-onset diabetes (JOD) is considered to have a polygenic inheritance modified by environmental influences such as stress viral infections etc. Recently very in-

teresting data have been published concerning the inheritance of patients with MODY (18). In contrast to JOD it could be shown that most patients with MODY had a diabetic parent and half of the cases showed direct vertical transmission of diabetes through three generations suggesting an autosomal dominant inheritance. Furthermore of extreme importance are the observations that in the families with the MODY the diabetes remains very mild in most cases without insulin and that severe long-term vascular complications are rare (7). The above-mentioned prognostic data of Rosenbloom et al. (16) would be more meaningful if information of the inheritance was available.

2. *Pathogenetic role of peripheral insulin resistance?*

Hyperinsulinemia during glucose tolerance tests (1) in non-obese children with asymptomatic diabetes has been taken as evidence for the existence of peripheral insulin resistance. In our experience decreased or absent insulin responses are the usual finding (19). This could either mean a primary beta-cell insufficiency or hypothetically a result of a long standing peripheral resistance causing beta-cell "exhaustion". We investigated some non-obese patients with asymptomatic diabetes and found no evidence for insulin resistance (9, 19). At variance with our finding are those of other authors demonstrating insulin resistance in chemical diabetes (8), but the experimental protocol is difficult to evaluate (2). Thus different opinions exist in this matter but Cerasi and Luft state that "if some degree of insulin resistance is present in early diabetes it probably acts as a secondary additive factor rather than a primary one" (2).

TREATMENT

It is not astonishing that authorities in this field have divergent opinions regarding the treatment of choice because of the great fluctuation of the natural history of the disease. However agreement exists concerning one point, if obesity is present it should be treated. This measure will ameliorate glucose tolerance (3). Anecdotal observations of successful treatment with sulfonylurea are available but the observed effects can be explained by the normal fluctuation of the disease (16). Jackson advocates insulin treatment in the late stages of asymptomatic diabetes in order to restore pancreatic function and perhaps induce remission periods over many years well controlled with small insulin doses (11, 17). In Linköping we follow the advice of Jackson, which is also supported by experimental evidence (20). It remains to be shown however if early insulin treatment delays diabetic vascular complications.

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Department of Pediatrics
University Hospital
S-581 85 Linköping
Sweden

DISCUSSION

Ole Ortved Andersen Have tissue types been determined in patients with MODY?

Anders Häger Yes but to my knowledge no significant association has been found between HLA types and MODY

INFLUENCE OF DIABETES ON METABOLISM OF VASCULAR SMOOTH MUSCLE

HANS J ARNQVIST

Department of Pharmacology and Department of Internal Medicine
Linköping University Linköping S d n

ABSTRACT Glucose utilization and the conversion of glucose to lactate CO_2, glycogen and lipids are decreased in the aorta from diabetic rats and rabbits. In addition the incorporation of amino acid into protein is reduced in diabetic rat aorta. The metabolic changes produced by diabetes are counteracted by insulin treatment, but there is a time lag of about 2 days before the effect of insulin treatment appears. The membrane transport of glucose in smooth muscle is carried out by a specific transport system of the facilitated diffusion type A rate limiting influence of membrane transport on glucose metabolism is found in bovine mesenteric arteries and rabbit colon smooth muscle. In these preparations the influence of glucose concentrations on glucose metabolism is most pronounced in the range 0–11.1 mmol exhibiting saturation at higher glucose concentrations. Insulin in high concentration (0.1 U/ml) has acute (<3 h) metabolic effects *in vitro* on smooth muscle which are qualitatively similar to those in skeletal muscle, but are weaker and appear later The threshold concentration for the acute metabolic effects of insulin on smooth muscle *in vitro* is 10–100 times above the physiological levels, indicating a low acute sensiti ity to insulin.

KEY WORDS: Vascular smooth muscle, metabolism, diabetes mellitus, insulin, glucose concentration

The role of the local metabolism of vascular tissue in the development of degenerative vascular diseases has received increasing at tention in recent years (?1 27) In diabetes mellitus a metabolic abnormality is associated with vascular disorders and it is possible that diabetic angiopathy could be a consequence of an altered metabolism of the vascular wall. It is therefore of interest to know how the local metabolism of the vascular wall is influenced by the diabetic state and to elucidate the cause of the metabolic changes

The vascular lesions in diabetes express themselves as an increased frequency of atherosclerosis and as a microangiopathy of the capillaries and small blood vessels which is virtually pathognomonic (for ref see Bradly (9)) Metabolic studies on capillaries and small blood vessels are subjected to technical problems which are still unsolved in many respects Larger arteries can be dissected free from surrounding tissues and used for metabolic studies *in vitro* with conventional methods. The major cell type of larger and medium sized arteries is the smooth muscle cell and metabolic data obtained on such arteries reflect therefore mainly the metabolic activity of smooth muscle. According to recent data smooth muscle cells besides their contractile function synthesize extracellular structural components of the vascular wall such as col lagen, elastin and mucopolysaccharides (13 20 25) Proliferation of smooth muscle cells has been implicated as a major event in the pathogenesis of atherosclerosis (21)

EFFECT OF DIABETES

An impaired glucose metabolism has been re peatedly demonstrated in vascular smooth

muscle of diabetic animals when vascular preparations of control and diabetic animals are exposed to the same glucose concentration *in vitro*. In aortic tissue of alloxan-diabetic rats and rabbits, the total glucose utilization and the conversion of glucose to CO_2, lactate, glycogen and lipid are markedly depressed (18, 23, 24). In aorta from the spontaneously diabetic Chinese hamster similar changes in glucose metabolism are found (9).

Ben-Tor and Wertheimer (7) reported that the incorporation of amino acid into protein was decreased in alloxan-diabetic rat aorta. This observation has been confirmed by this author (Arnqvist, to be published). From Fig. 1 it can be seen that a marked reduction in the incorporation of leucine-^{14}C into protein was found in streptozotocin diabetic rat aorta 2 weeks after the induction of diabetes, and after a duration of diabetes of 5 weeks this reduction was even more pronounced. The rate of incorporation of amino acid into protein is considered to reflect the rate of protein synthesis. The reduced incorporation of amino acid into protein therefore suggests a decreased protein synthesis in diabetic aorta *in vitro*.

Insulin treatment of alloxan-diabetic rabbits and spontaneously diabetic Chinese hamsters for 2–3 days has been shown to normalize the impaired aortic glucose metabolism (10, 18). The time course for the effect of insulin treatment on glucose metabolism in diabetic rabbit

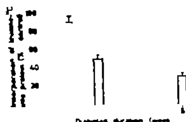


Fig. 1. Effect of duration of diabetes on incorporation of leucine-^{14}C into protein in rat aorta. Control and diabetic aortas were incubated for 180 min in the presence of ^{14}C-labelled leucine and the amount of radioactivity incorporated into protein was then determined. Mean ±S.E. (6–8).

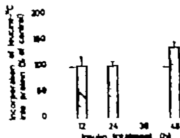


Fig. 2. Effect of insulin treatment on leucine-^{14}C incorporation in diabetic aorta. Two weeks after the induction of diabetes the rats were given 6–8 U of an intermediate acting insulin once a day. Untreated diabetic rats were used as control. 12, 24 and 48 h after the start of insulin treatment the incorporation of leucine-^{14}C into protein in rat aorta was determined *in vitro* during an incubation period of 180 min. Mean ±S.E.

aorta has been studied by Mulcahy and Winegrad (18). They found no effect of insulin treatment after 18 h while a significant effect was found after 42 h. After 48 h the metabolism had returned to normal. The reduced incorporation of amino acid into protein in aorta of streptozotocin diabetic rats was increased by insulin treatment for 48 h whereas no effect was found after 12 or 24 h (Fig. 2) (Arnqvist, to be published).

EFFECT OF GLUCOSE CONCENTRATION

The metabolism of blood glucose involves diffusion of glucose through the extracellular space to the cell membrane, transport across the cell membrane and intracellular degradation. The influence of glucose concentration on glucose metabolism is dependent on the kinetic characteristics of the step which is rate limiting for glucose utilization.

Diffusion of glucose to the cell membrane probably has a rate-limiting influence only at very low glucose concentrations (6).

In smooth muscle as in skeletal muscle glucose is transported across the cell membrane by a specific transport system of the facilitated diffusion type (for references see 6, 8). In bovine mesenteric artery, a medium sized artery with a high content of smooth muscle and in rabbit colon smooth muscle the membrane transport of glucose is rate limiting for

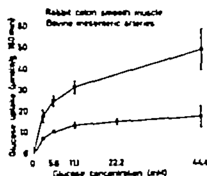


Fig 3 Effect of varying glucose concentrations (2.8–44 4 mmol) on the glucose uptake in bovine mesenteric arteries ($n=11$) and rabbit colon smooth muscle ($n=7$). The glucose uptake was determined after an incubation period of 180 min. Mean ± S.E. From Arnqvist (3). Reproduced with permission from Acta physiol. scand.

utilization during *in vitro* conditions (1 2) while membrane transport of glucose may not be rate limiting in rabbit aorta (26)

The influence of glucose concentration on total glucose utilization in bovine mesenteric arteries and rabbit colon smooth muscle for *in vitro* conditions is shown in Fig. 3 From the figure it can be seen that the glucose uptake exhibited saturation kinetics the effect of increasing glucose concentration being most pronounced within and just above the physiological range Increasing glucose concentrations had a similar effect on lactate content *lactate production and glycogen content in* these tissues (3)

The major pathways of glucose metabolism in smooth muscle require an initial phosphorylation of glucose to glucose-6-phosphate (17) According to the available data the phosphorylation of glucose in vascular smooth muscle is brought about by typical hexose kinases with high affinity for glucose (Km 0 01–0 4 mM) (6) Because of the low Km of the hexose kinase reactions phosphorylation would be expected to be saturated if intracellular glucose is present at concentrations near or equal to the physiological blood glucose concentration.

Intracellular glucose can be metabolized to some extent without phosphorylation to sorbitol via the polyol pathway (for references see 26) The polyol pathway has been suggested as a mechanism by which hyper glycemia could cause the late complications of diabetes The enzymes of this pathway are present in vascular tissue. Winegrad et al (26) have reported that in normal rabbit aorta a small amount of glucose is metabolized to sorbitol and that the sorbitol production is increased by elevated glucose concentrations. However there is no report of an increased sorbitol content or an increased sorbitol production in diabetic vascular tissue.

EFFECT OF INSULIN

Moderate acute effects of high concentrations of insulin can be demonstrated *in vitro* in several smooth muscle preparations. In rat and rabbit aorta effects of insulin (0 1 U/ml) on glucose metabolism have been reported (18 24) In bovine mesenteric arteries rabbit colon smooth muscle and human intestinal smooth muscle insulin (0 1 U/ml) stimulates monosaccharide transport amino acid transport,

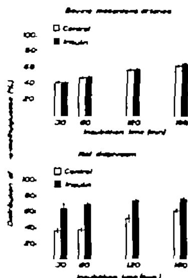


Fig 4 Effect of insulin (0.1 U/ml) on the distribution of ^{14}C-labelled 3-0-methylglucose (10 mmol) in bovine mesenteric arteries (=10) and intact rat hemidiaphragm (=5) A significant ($p<0.01$) increase in 3-0-methylglucose distribution was found after 180 min in bovine mesenteric arteries and after 30 min in rat diaphragm. Mean ± S.E. From Arnqvist (2) Reproduced with permission from Acta physiol. scand.

glycogen synthesis and incorporation of amino acid into protein (2, 4, 5). The effects of insulin on these metabolic parameters appeared late and were moderate in comparison with the corresponding effects in skeletal muscle (6). Fig. 4 shows the effect of insulin on the membrane transport of the glucose analogue 3-O-methylglucose in bovine mesenteric artery and for comparison also in rat diaphragm, which is a commonly used skeletal muscle preparation. In bovine mesenteric artery a small significant effect of insulin was found after 3 h while in rat diaphragm a marked effect of insulin was found after 30 min.

The dose–response relationship for the action of insulin on smooth muscle has been studied in bovine mesenteric arteries (4), rabbit colon smooth muscle (1) and the detrusor muscle of rat urinary bladder (8). Fig. 5 shows the dose–response curves obtained on ^{14}C-glucose accumulation and incorporation of leucine into protein in bovine mesenteric arteries. The effect of insulin on rat diaphragm determined with the same technique is also given. From the figure it can be seen that the dose–response relationship was similar for both parameters in bovine mesenteric arteries and also in rat diaphragm. In comparison with rat diaphragm the dose response curves for bovine mesenteric arteries were displaced to the right, indicating a lower acute sensitivity to insulin. The threshold concentration for these effects of insulin on bovine mesenteric arteries was 10^{-3} U/ml. In rabbit colon smooth muscle the threshold concentration for the effect of insulin on glucose ^{14}C accumulation was 10^{-3} U/ml (1) and the same threshold concentration was found for the effect of insulin on monosaccharide transport in the detrusor muscle of rat urinary bladder (8). The hormone concentrations at which metabolic effects of insulin can be demonstrated on smooth muscle during *in vitro* incubations for a few hours are therefore 10–100 times above the physiological range (10^{-}–10^{-4} U/ml).

The available results thus suggest that insulin in high unphysiological concentrations has

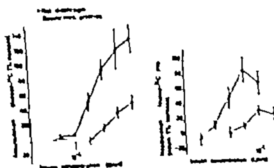


Fig. 5. (A) Dose–response relationship for the effect of insulin on the accumulation of ^{14}C-glucose in bovine mesenteric arteries and rat diaphragm (n=4–8). All tissue samples were incubated for 180 min in 5.6 mmol glucose-^{14}C. To make the weak effect of insulin on bovine mesenteric arteries more easy to evaluate the extracellular ^{14}C-glucose was washed out by incubating the arteries for a further period of 30 min in a medium of the same composition but with unlabelled glucose. (B) Dose–response relationship for the effect of insulin on the incorporation of leucine-^{14}C into protein in bovine mesenteric arteries (n=8–12) and rat diaphragm (n=6–11). The tissue samples were incubated for 180 min in 0.01 mmol leucine-^{14}C and 11.1 mmol glucose. Mean ± S.E. From Arnqvist (4). Reproduced with permission from Acta physiol. scand.

metabolic effects on smooth muscle which are qualitatively similar to those in skeletal muscle (6, 12, 19). However smooth muscle has a low sensitivity to insulin and it has not been possible to demonstrate any acute (≤3 h) metabolic effects of insulin on smooth muscle at physiological hormone concentrations.

EFFECT OF INSULIN AND DIABETES ON PROLIFERATION OF SMOOTH MUSCLE CELLS

The influence of insulin and diabetic serum on the proliferation of smooth muscle cells has been studied in tissue culture. Stout et al. (22) investigated the effect of insulin on the growth of smooth muscle cells from thoracic aortas of 1 year old monkeys. According to their results insulin in physiological concentrations had a weak growth-promoting action on smooth muscle cells with a few passages in tissue culture (young cells) but had no effect on cells that were older in culture [illegible] or nine passages). Ledet et al. [illegible]

that the growth of rabbit aortic smooth muscle cells was stimulated by diabetic rabbit serum. The growth promoting factor in diabetic serum was neither glucose nor hyperlipidemia. Also human serum from patients with juvenile diabetes stimulated the growth of rabbit aortic smooth muscle cells (14 15) Ledet found a slight growth promoting effect of growth hormone on smooth muscle cells from rabbit aorta while insulin had no significant effect.

Since insulin was found to have a growth promoting effect on smooth muscle cells from monkey aorta but not on cells from rabbit aorta the results are inconclusive It should be mentioned that there may be considerable species variation in insulin effects (11) Studies on human arterial smooth in tissue culture would therefore be of great interest.

In aortic tissue removed from diabetic animals an impaired metabolism is found during *in vitro* conditions (cf page 107) while diabetic serum according to Ledet (14) has a growth promoting effect on aortic smooth muscle cells. These results does not seem to agree since cell proliferation would be expected to be associated with an augmented metabolic activity of the smooth muscle cells. The reason for the anomalous results is not clear and require further studies.

ACKNOWLEDGEMENT

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Department of Pharmacology and
Department of Internal Medicine
Linköping University
Linköping
Sweden

[illegible]LAR DISEASE

[illegible]erglycemia and Hypophosphatemia [illegible] Unloading[1]

[illegible]

[illegible] of Medicine Department of Pediatrics [illegible] Regional Hospital, Aalborg, Denmark

ABSTRACT [illegible] impairment in oxygen transport of the erythrocytes [illegible] hyperglycemia by the formation of glycosylated hemoglobin (HbA[illegible]) and [illegible] factors of glycolysis i.e. hypophosphatemia and [illegible] of red cell 2,3-diphosphoglycerate. Diabetic angiopathy may be the ultimate result of [illegible] microvascular responses to discrete hypoxic injuries associated with increased plasma permeation through the vessel walls. It is shown that two additional risk factors for atherosclerosis—smoking and hypertriglyceridemia may also lead to arterial [illegible] changing the position of the oxyhemoglobin dissociation curve.

KEY WORDS. Diabetic angiopathy, red cell oxygen unloading, oxyhemoglobin dissociation curve, 2,3-diphosphoglycerate, plasma inorganic phosphate, insulin

With the introduction of insulin in the treatment of diabetes it was hoped that all the problems in diabetic management had been resolved. However as the disease changed from an almost acute lethal condition to a chronic fluctuating metabolic disturbance the problem of diabetic vascular disease became increasingly apparent. Vascular lesions and impairment of the circulatory system is the main challenge to research on diabetes today.

The typical lesions in juvenile diabetics involve the small blood vessels (arterioles, capillaries and venules) in such diverse tissues as the retina, the renal glomeruli, muscle and the skin. In addition there occurs an acceleration of atherosclerosis. It is the purpose of this paper to draw attention to the possibility that tissue hypoxia may be an important pathogenetic factor in the development of diabetic angiopathy. Evidence for this statement will be provided first by comparing the various diseases in which the characteristic features of diabetic retinopathy occur and second by presenting data which show that diabetes by influencing the metabolism of the erythrocytes produces a fluctuating disorder of oxygen transport. This disorder is present from the early onset of the disease and is a consequence of the combination of a high blood glucose level and absolute or relative hypophosphatemia induced by exogenous insulin. The results emphasize that efforts in the treatment of diabetes should be directed along lines which will enable us to mimic Nature to a degree not achieved by present methods which include the injection of insulin once or twice a day. The data exemplify how an insulin insensitive cell can be affected in the diabetic environment and suggest that similar meta-

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bolic changes may occur in other insulin insensitive cells such as endothelial cells platelets and parts of the retina.

Retinal tissue hypoxia—a common factor for retinal changes

Diabetic retinopathy is the initial vascular complication that occurs, and it can be directly observed and followed with the ophthalmoscope It has therefore become the corner stone in the study of diabetic microangiopathy The retinopathy is characterized by changes primarily in the venules and capillaries, subsequently in the arterioles and with neovascularization as another important feature The work of Norman Ashton (2, 3) has shown clearly that the various pathologic features of retinopathy are not specific for diabetes Microaneurysms with similar hyaline thickening, lipid and mucopolysaccharide staining have been described in many conditions such as retinal vein thrombosis hyperviscosity syndrome as seen in macroglobulinemia and myelomatosis, pulseless disease sickle cell anemia and malignant hypertension. Diabetes however stands out as being the disease in which microaneurysms are seen most frequently in greatest number and in the most advanced forms giving rise to hemorrhages and exudates. On closer scrutiny retinal hypoxia may be the common factor for microaneurysm formation in these conditions. The mechanism of the formation of microaneurysms in retinal vein occlusion and in macroglobulinemia appears fairly clear and differs only slightly from each other The common factor is venous stasis produced either by venous occlusion or by the highly viscous blood due to the presence of macroglobulins in the plasma. In both cases hypoxia of the retinal tissue is produced leading to endothelial proliferation in the venous microcirculation and to microaneurysm formation. Other diseases in which microaneurysms have been described such as pulseless disease and sickle cell anemia, are conditions which lead to rheologic changes in the retinal microcirculation and probably to retinal hypoxia. Thus a comparison of the pathologic features in diabetic retinopathy with other retinopathies suggests that hypoxia may be a common factor for the development of these retinal changes. If this is so then the retinal tissue must be very sensitive to hypoxia. In this respect it should be remembered that the retinal vessels do not have an adrenergic sympathetic nerve supply and variations in blood supply can occur only through autoregulation which may be controlled by local factors such as pH carbon dioxide tension and especially oxygen tension. It is well known that the retinal vessels in man are very responsive to variations in oxygen tension. Cusick and co-workers (8) first reported that the retinal vessels dilate at low ambient oxygen tensions and constrict at high tensions and this finding has been confirmed by many investigators (26 31) The response to oxygen is apparent within a minute and is unaffected by thoracic sympathectomy The mechanism by which changes in blood oxygen bring about changes in the caliber of the small blood vessels is not understood. Conceivably the endothelial cells themselves respond to variations in oxygen tension. Experimentally in rats Cunha-Vaz (7) has shown that elevation of the intraocular pressure leading to ischemic episodes from 30 min to 3 hours or venous stasis for 3 to 4 hours is enough to produce a breakdown of the blood-retinal barrier which is a function of the retinal endothelial cells. He could also show that these short episodes produced swelling and degeneration of the endothelial cells on the arterial side and proliferation of the endothelium on the venous side. Therefore, the retinal endothelium seems highly dependent upon and highly sensitive to variations in oxygen tension and apparently these cells are adapted to a special level of oxygenation. The effect of hypoxia may be increased in the diabetic individual since there is evidence that the diabetic retina has an increased oxygen requirement. Periodic retinal hypoxia over many years in combination with metabolic disturbances in the retinal →

0 001) (11 13) This effect is particularly pronounced in severe cases of type IIB type IV type V as well as in the rare type I hyperlipoproteinemia (HLP) Induced hyperlipidemia has been shown to reduce tissue oxygen tension in man (27) An even modest hyperlipoproteinemic reduction in arterial wall oxygen tension could impair the metabolism and transport of lipoproteins in the wall and thereby generate a vicious cycle which could eventually seriously accelerate atherogenesis

Astrup et al (4) discovered that a large number of patients with occlusive arterial wall diseases also had a significant leftward shift in their ODC. They found that these affected patients were smokers and that the alteration in the ODC resulted from inhalation and absorption of the carbon monoxide found in tobacco smoke. They suspected that the shifted ODC resulted in hypoxia of the arterial wall tissue However this possibility could not be quantified. More recently Ditzel (16) studied the effect of smoking on the oxygen release capacity of erythrocytes in a group of healthy twenty year old men of normal weight. The young men were either non-smokers or smokers the latter being defined by their smoking more than 8 cigarettes per day Although all individuals were examined in the fasting state early in the morning the P_{50} at actual pH was significantly reduced in the 19 smokers when ... 1 to the 24 non-smokers. Heart rate hemoglobin concentration and red cell 2,3-DPG did not differ in the two groups Using a computer simulation of the arterial wall oxygen transport system the ODC and anemic effects on both of the mural oxygen supply routes luminal and adventitial have been assessed (30) With 5% CO Hb produced by smoking approximately 20 cigarettes per day both the endothelial and minimum PO_2 were reduced by about 2 mmHg. But with 20% CO Hb produced by approximately 60 cigarettes per day the P_{50} was reduced by 6 mmHg and both the endothelial and minimum PO were reduced by about 9 mmHg. This alone represents a considerable reduction in oxygen availability and in combination with other factors may represent a serious insult. Astrup (5) has shown experimentally that carbon monoxide like arterial hypoxia can influence the permeability of the arterial endothelium to macromolecules including lipoproteins and that carbon monoxide can accelerate the atherosclerotic process

Thus the studies have shown that in diabetics a complex disturbance occurs in the erythrocytes leading to increases in the affinity of oxygen to hemoglobin. Hyperglycemia leads to increased amounts of a glycohemoglobin hemoglobin A_{1c} with increased oxygen affinity and the oxyhemoglobin equilibrium may also be disordered by transient decreases in Pi following insulin administration High concentrations of triglyceride-rich lipoproteins and smoking will also impair erythrocytic oxygen transport The only way to prevent these changes in our present state of art is to regulate our diabetics as well as possible to avoid smoking and to lower the content of saturated fat in the food.

Supportive therapeutic trials

These studies suggest however that red cell metabolism in diabetes may be influenced by the concentration of plasma inorganic phosphate (Pi) Elevated levels of Pi may result in an increase in red cell 2,3-DPG and a normalization of the ODC. In order to arrive at an optimal oxygen release capacity of the red cells containing increased proportion of hemoglobin A_{1c} it may be pertinent to maintain high levels of Pi and red cell 2,3-DPG In order to validate this supposition experimentally a diphosphonate known to enhance tubular phosphate reabsorption in man, was given to 14 insulin treated diabetic and healthy volunteers for 28 days. The diphosphonate was found to increase significantly both Pi and the P_{50} at *in vivo* pH (23) In another study a dietary supplement of dibasic calcium phosphate was given to 34 non acidotic ambulatory diabetic children providing approximately double the amount of phosphorus and calcium as in the

standard diabetes diet. With this dietary supplement the mean P_{50} value increased significantly (12, 14)

At the present time we are involved in prolonged careful evaluations of such regimens in order to assess their effectiveness. It is hoped that these experiences will lead to methods of preventing diabetic angiopathy

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Department of Medicine
Aalborg Regional Hospital
Box 561
DK-9100 Aalborg
Denmark

DISCUSSION

Karl-Martin Lundmark. Are there any data on the determination of the HbA_{Ic} in diabetic children?

Jørn Ditzel As far as I know only one pediatrician Professor Elsa Paulsen Dept. of *Pediatrics University of Virginia, Charlottes* ville has extensive experience with hemoglobin A_{Ic} in children I can refer to the proceedings of a conference on diabetic microangiopathy which was published as Suppl. 2 to *Diabetes 25* 890 1976 in which Elsa Paulsen discusses the determination and the level of hemoglobin A_{Ic} in insulin-dependent juvenile diabetics

Johnny Ludvigsson Is HbA_{Ic} mainly related to the mean value of blood glucose or does it also reflect the glucose variations. This is of interest as it may be possible to have a labile metabolism with great variation of blood glucose for some weeks still giving an almost normal mean value of glucose

Jørn Ditzel HbA_{Ic} reflects the average blood glucose levels. Depending on the amount of HbA_{Ic} the oxyhemoglobin dissociation curve will be influenced in the direction of a left shift (increased oxygen affinity to hemoglobin) The decrease in blood glucose which follows insulin administration lowers the content of inorganic phosphate in the plasma and consequently the amount of 2,3-diphosphoglycerate in the red cell This mechanism will also induce a left shift of the oxyhemoglobin dissociation curve. The example you suggest with a labile fluctuating blood sugar will in a diabetic always give abnormally high mean value of blood sugar and therefore increased amounts of HbA_{Ic}.

Niels Schwartz Sørensen Is it difficult to carry out the analysis of HbA_{Ic}? What is your method?

Jørn Ditzel It is not difficult only laborious, to carry out the analysis of HbA_{Ic}. The method we are using is a slight modification of the method described by Schwartz et al (*Diabetes 25* 1118 1976) It is a column chromatographic method using the resin Biorex 70.

Claes Hellerström Proliferation of smooth muscle cells is a characteristic feature of the atherosclerotic plaque Do you know if low oxygen tension is an adequate stimulus for this reaction?

Jørn Ditzel Several investigations on the isolated smooth muscle cells of the aorta have shown that when these cells are exposed to low oxygen tension they proliferate Their uptake of low density lipoproteins will increase but the degradation will simultaneously decrease thus transforming them into foam cells (Albers J J & Bierman E. L. *Biochem Biophys Acta 224* 422 1976)

SYNTHETIC PATHS TO INSULIN

J MARKUSSEN

From the Laboratory of Peptide Chemistry Novo Industri A/S

ABSTRACT The methods for synthesizing insulin molecules are surveyed and listed in four categories. Illustrative examples in each category are described.

KEY WORDS: Insulin, peptide chemistry synthesis, semisynthesis, disulfide bonds

In the study of the insulin molecule at the molecular biological level structure-function relations receptor binding, immunogenicity and immunochemical reactions insulin analogs are useful. Due to the complicated structure of insulin with 2 chains, the A and B-chains, linked with 2 disulfide bonds (A7–B7 and A20–B19) and an additional intrachain disulfide bond in the A-chain (A6–A11) the known insulin syntheses are limited and can be listed in four categories.

I. Disulfide bond formation by a combination of the A and B-chains in a random fashion.

II. Disulfide bond formation by a combination of the chains in a determined fashion where a bridge connects the chains and renders the correct disulfide bond formation a monomolecular process. As a result the yields increase

The bridge must be removable without causing damage to peptide and disulfide bonds.

III. Total synthesis i.e. stepwise synthesis of all peptide and disulfide bonds in an unambiguous manner by which the primary structure of insulin is proven to be correct.

IV Semisynthesis, i.e. replacement of amino acids or peptide fragments by synthetic and/or enzymatic means.

Abbreviations.

A	A-chain of insulin
Acm	acetamidomethyl
B	B-chain of insulin
Boc	tert. butyloxycarbonyl
Bpoc	2-(p-biphenylyl)-isopropyloxycarbonyl
But	tert. butyl
DCC	dicyclohexylcarbodiimide
DOI	desoctapeptide-B(23–30) insulin
Dsa	2,7 diamino-suberic acid
HOBt	1-hydroxybenzotriazol
OBut	tert. butylester
ONSu	N-hydroxysuccinimide ester
OTcp	2,4,5-trichlorophenyl ester
Tfa	trifluoracetyl
Trt	triphenylmethyl

I COMBINATION OF A AND B-CHAINS

The chain combination by a random disulfide bond formation is the oldest and due to its simplicity the most widely used process The drawbacks are low yields and many by-products. The chemistry is shown in Fig. 1 The chains *featuring the cysteine residues in the* S-sulfonated forms ($S\text{-}SO_3^-$) are prepared either from synthetic chains or natural insulin. When insulin is treated with a sulfite salt and an oxidizing reagent (e.g. $Na_2S_4O_6$) the disulfide bonds are broken and the S-sulfonated chains are formed. The S-sulfonated forms of the chains are stable and suitable for separation and purification.

The reversed process from

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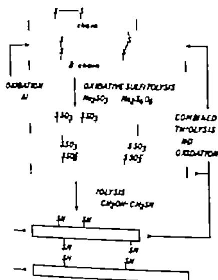


Fig 1 Preparation of the S-sulfonated A- and B-chains by oxidative sulfitolysis of insulin, transformation to sulfhydryl chains by thiolysis, and resynthesis of insulin.

product isolated after a minimum of work-up (7 8, 13) which might have caused some purification. Very few authors have presented yields in the classical sense i e, as weight percent of analytically pure insulin (1)

The terminology of the combinations is as follows,

(*a*) both chains are natural, resynthesis or recombination,

(*b*) one chain is natural the other is synthetic: partial synthesis

(*c*) both chains synthetic full synthesis

(*d*) chains from two species, hybrid insulin

The development of the combination technique and its applications are summarized in Table 1

II. COMBINATION WITH A REMOVABLE BRIDGE LINKING THE CHAINS

The elucidation of the structure of proinsulin as a single chain molecule having a peptide link from the B30 to the A1 terminals of insulin and the demonstration of the ability of thiolysed proinsulin to reoxidize in high yields (19) gave rise to the "mini-proinsulin" concept, i e Insulin molecules linked from the α-amino group of Gly A1 to the ε amino group of Lys B29 These two amino groups are in proximity in the rhombohedral insulin crystals (?) It was found that cross-linking with dicarboxylic acids (oxalic acid adipic acid suberic acid) gave products that could be thiolysed and reoxidized in high yields (3 21) A dicarboxylic acid bridge cannot be removed from the "mini-proinsulin" rendering insulin but three removable bridges have been sug

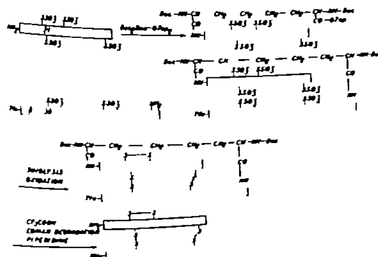


Fig 2 Synthesis of insulin from the S-sulfonated A and B chains [illegible] mini pr[illegible]insulin with [illegible]able bridge

Table 1 *Development and applications of combination methods*

Year	Reference	Accomplishment	Combination process	Yields %	Comments
1960	6	First combination, natural chains	Thiolysis of a mixture of S-sulfonated chains	1–2	Bioassays without purification, *in vivo in vitro*, immunochemical
1961	7	First combination, isolation of crystals, natural chains	Thiolysis with thioglycolic acid of S-sulfonated chains/oxidation by air	5–10 ~3	Specific activity of crude products *in vivo*. Crystals
1962	20	First hybrid insulins and/or immunological applications	Thiolysis of a mixture of S-sulfonated chains. Oxidation by air	0.5–5	Bioassays without purification, *in vitro*
1963 1964	11 12	First partial synthesis. Sheep insulin	Thiolysis of a mixture of S-sulfonated chains. Oxidation by air	0.3	Low yields accounted for by defectiveness of the synthetic chains
1963	14	First full synthesis. Sheep insulin		1–2	Low yields accounted for by defectiveness of the synthetic chains
1963	8	Improved combination procedure	Air oxidation of sulfhydryl chains at pH 10.6. 50% excess of A-chain	~50	Yields given as specific activity of crude product. *In vivo*
1965/66	13	First full synthesis with crystals isolated. Bovine insulin	Air oxidation of sulfhydryl chains at pH 10.6. 50% excess of A-chain	1.2–2.5 ~0.1	Specific activity crude product Crystals
1966	12	Improved purification method from combination mixtures	500% excess of A-chain	30–50	Yield calculated on the basis of the amount of B-chain in combination
1975	1	Oxidation of sulfhydryl chains and removal of thiol reagent combined	Buffer exchange on a Sephadex G-25 column at pH 10.6	4.2 10–15	Synthetic sheep A-chain. Natural chains. Chromatographically pure insulin

disulfides is carried out via thiolysis of the S-sulfonated chains with an excess of a thiol e.g. mercaptoethanol producing the sulfhydryl forms of the chains. Having removed the excess of thiol and mixed chains oxidation with air produces among many by-products and in moderate yields insulin (6 7).

In a variation of the combination procedure (7 12) only the S-sulfonated A-chain is converted to the sulfhydryl form and then brought to reaction with the S-sulfonated B-chain (arrows right side of Fig 1). Insulin is formed in a process which is formally a thiolysis of the B7 and B19 S-sulfonates by the thiol groups of the A7 and A20 cysteines and an oxidation of the A6 and A11 thiols to a disulfide bond.

One A-chain and one B-chain can be visualized as combining into 12 isomer compounds only one of which features the disulfide bonds of insulin. Other by-products arise if two identical chains combine. A major cause of by-product formation is the tendency of the B-chains to combine and form insoluble polymers. In order to suppress this reaction some authors use an excess of from 50% (8) to 500% (12) of the A-chain in relation to the B-chain.

Determination of the yield of insulin in a combination reaction and comparison of various methods presents a problem. If only little material has been available the insulin has most often been determined by bio-methods using the reaction medium without any work up (6 11 12 14 20). Yields have been represented as the specific activity (U/mg) of a

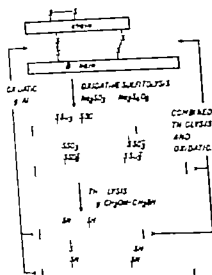


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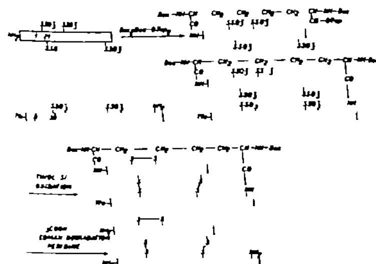
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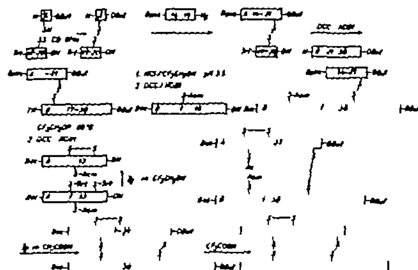


Fig 3 Total synthesis of human insulin.

gested. carbonylbis(L-methionyl) removable with CNBr (5) 2,2 sulfonylbis(ethoxycarbonyl) removable at 0°C with 0.5 M NaOH within seconds (15) and 2,7-diamino-suberoyl removable with phenyl isothiocyanate in the Edman degradation fashion known from protein sequencing (4 9)

The steps involved in synthesizing insulin via 2 7-diaminosuberoylinsulin (9) are shown in Fig. 2. The diaminosuberic acid is introduced with the amino groups protected by Boc groups and the carboxyl groups activated as OTcp esters Boc$_2$-Dsa-OTcp$_2$ The bifunctional reagent in excess is mixed with S-sulfonated A-chain and couples to the α-amino groups of Gly A1 After removal of excess reagent the second OTcp ester of the product is coupled to the ε-amino group of Lys B29 of a S-sulfonated B-chain having the α-amino group of Phe B1 protected by the Tfa group After thiolysis of the S-SO$_3^-$ groups with mercaptoethanol the disulfide bonds are closed by oxidation with air Removal of the 2 Boc groups with trifluoracetic acid exposes the amino groups of the diaminosuberoyl link, which is then removed in an Edman degradation cycle Finally treatment with a weak base (0.1 M piperidine) removes the Tfa protecting group from Phe B1 and yields insulin. The yields from the cross-linked S-sulfonated chains to Tfa-insulin are 20–40%

III TOTAL SYNTHESIS

The total synthesis of human insulin with a predetermined formation of the 3 disulfide bonds was recently accomplished (17 18) Fig. 3 shows the crucial steps. An asymmetric disulfide A(20–21)-B(17–20) is synthesized by thiolysis with Cys A20 of the sulfenylthiocarbonate of Cys B19 The formed disulfide bond serves as a "bridge" between the growing chains throughout the synthesis The fragment Bpoc-A(14–19)-N$_3$ is coupled to the free amino group of A20 with an azide coupling. The free carboxyl group of B20 is coupled with DCC/HOBt to the free amino group of the otherwise fully protected fragment B(21–30) The product Bpoc A(14–21)-OBut Trt-B(17–30)-OBut is treated with HCl in trifluorethanol at an apparent pH of 3.5 (glass electrode) and the most acid labile group the trityl group of B17 is removed selectively Bpoc A(14–21)-OBut B(17–30)-OBut is coupled with DCC/HOBt to the free carboxyl group of B16 in the otherwise fully protected fragment Boc-B(1–16) The cysteine residue B7 is introduced protected by the Acm group Before coupling to Boc A(1–13) the Bpoc group of A13 is removed selectively in 60°C trifluorethanol.

The fragment Boc A(1–13) has been prepared with Cys A6 and A11 protected by the trityl group and Cys A7 by the Acm group.

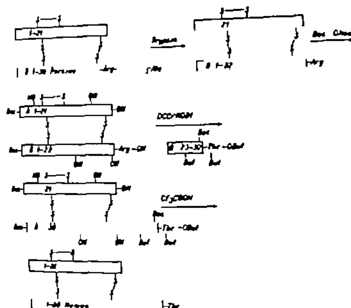


Fig 4 Semisynthesis of human insulin from porcine insulin.

Treatment with iodine in trifluorethanol or in hexafluorisopropanol oxidizes selectively the S-trityl groups of A6 and A11 to the disulfide bond A6–A11 but leaves the S-Acm group intact. The free carboxyl group of A13 of the fragment of Boc A(1–13) prepared in this way is coupled with DCC/HOBt to A(14–21)-Boc B(1–30) to produce a fully protected Boc A(1–21)-Boc-B(1–30) The protecting groups (except for the Acm s of Cys A7 and B7) are removed with trifluoracetic acid The third and last disulfide bond, A7–B7 is formed by oxidation of the S-Acm groups with iodine in acetic acid.

IV SEMISYNTHESIS

An illustrative example among the semisynthetic insulin syntheses is the preparation of human insulin from porcine insulin (16) Fig. 4 shows the steps involved in replacing B30 alanine in porcine insulin with the B30 threonine of human insulin. Degradation with trypsin splits insulin at arginine B22 and yields desoctapeptide B(23–30)-insulin (DOI) Subsequent treatment of DOI with Boc-ONSu blocks the two α-amino groups (A1 and B1) The resulting Boc_2-DOI features 6 free carboxyl groups namely 4 γ-carboxylates (A4 A17 B13 and B21) and 2 α-carboxylates (A21 and B22) Coupling of Boc_2-DOI with an equimolar amount of synthetic human octapeptide B(23–30) with free N-terminal amino group but otherwise fully protected would if all 6 carboxyl groups reacted to the same degree produce the desired product with *one* new peptide bond, B22–B23 in a yield of 6 7% The reactivity of the carboxyl group of Arg B22 must, however be higher than that of the five others since yields of 25–40% of the partially protected human insulin are encountered Treatment with trifluoracetic acid removes the protecting Boc But and OBut groups and produces human insulin The over all yields from porcine to human insulin are in the range of 6–10%

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Laboratory of Peptide Chemistry
Novo Research Institute
Novo Allé
DK 2880 Bagsvaerd
Denmark

DISCUSSION

Anders Häger I want to ask a question about the present situation regarding the research on E coli synthesis of insulin as a result of a transfer of the code?

Jan Markussen I think "the state of art" allows for transfer of DNA to DNA of microorganisms whereas the production of the protein coded for is a goal yet to come

Jørgen Schlichtkrull Don Steiner has just told me about the successful transfer of pro-proinsulin DNA into E. coli However transcription or synthesis was not achieved The DNA was prepared from rat tumor mRNA and the structure determined wholly or to a large extent The next step would be to transfer the DNA coupled to a promoter for synthesis. If pre proinsulin or a part of it, can be synthetized we still have a series of problems e g. with maturation (i.e transformation to insulin) mutations isolation and purification, just to mention a few

TRANSPLANTATION OF THE ENDOCRINE PANCREAS

A. ANDERSSON

From the Department of Histology, University of Uppsala, Uppsala, Sweden

With the discovery of insulin in 1921 the prevention and successful treatment of diabetic coma and ketoacidosis became possible. However, as diabetic patients lived longer, previously unknown vascular complications affecting both large and small vessels developed. Thus, we are now some fifty-five years later confronted by the prevention and treatment of the vascular and nervous complications of long-term diabetes. According to a recent report of the National Commission on Diabetes to the U.S. Congress it is obvious that individuals with diabetes are 25 times more prone to blindness and 17 times more prone to kidney disease than those without diabetes. Furthermore these data indicate that there has been an increase in the magnitude of the problem during the last few years, since the prevalence and incidence figures suggest that the number of people with diabetes will double every 15 years.

The cause of complications in diabetes is still obscure but there is much evidence to suggest that if one could correct the metabolic defect completely and continuously by supplying insulin to the patient in physiological amounts the diabetic patient would achieve not only longevity but also freedom from cardiovascular-renal disease. New approaches to treatment of patients suffering from diabetes mellitus are obviously required in order to halt complications. No doubt one technique with much potential values is transplantation of the endocrine pancreas. There has, in fact, been a great deal of success in the development of these techniques in experimental animals, although it will undoubtedly last many years before they are accepted as a treatment for human diabetes. It is the aim of this presentation to review briefly the current status of endocrine pancreas transplantation and furthermore to present some of the investigations being carried out currently in our laboratory.

WHOLE-ORGAN PANCREATIC TRANSPLANTATION

In December 1966 R. C. Lillehei and collaborators at the University of Minnesota performed the first recorded pancreas transplantation to a diabetic patient. Since then there have been some fifty pancreas transplantations in the United States and a few European countries. To begin with, most of the attempted transplantations were done as pancreaticoduodenal grafts performed in conjunction with a kidney transplant. Due mainly to duodenal rejection there was a high morbidity and mortality. Therefore Gliedman transplanted the pancreas without the duodenum but with the pancreatic duct connected to one of the ureters. The results have been better with this approach and in the most successful case the patient survived for more than three years without insulin (13). Most of these patients had a kidney transplant as well, although in some of them the transplants were performed one at a time. The transplantation group at the

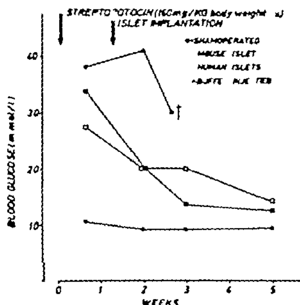


Fig 1 In a group of four nude mice three animals were made diabetic by means of an intravenous injection of streptozotocin. Two diabetics were transplanted intraperitoneally either with 570 allogeneic cultured mouse islets or 350 islets, which had been isolated from a human cadaveric pancreas and kept in culture for one week. The third hyperglycemic animal was sham-operated and died two weeks after the operation. The islet implanted animals decreased their blood sugars down to values not far from that of the control animal.

betic patient. From previous rough calculations it seems plausible to assume that about 50 000 medium-sized islets will be needed (20) To make possible successive collection of ets from several donors some kind of tissue k would therefore be most helpful

There are three possibilities for storage of isolated islets tissue culture at +37°C cold storage at +4–8°C The technique used in our laboratory for culture of isolated pancreatic islets (2, 4) has been extensively used both for transplantation purposes (3) and the elucidation of the regulatory mechanisms for insulin secretion and biosynthesis (1) As mentioned above this culture system has been found to be useful for storage of isolated human islets Cold storage at +4–8°C has so far only been attempted on rat (10 19) or mouse islets (12) but the results have varied The best results were obtained if the islets were maintained in tissue culture medium 199 with 18 mM glucose interrupted by a short period of warming to +37°C every week (12) Results from experiments with cryopreservation of isolated islets (10 29) or fetal pancreas (26) seem promising but there are still many methodological studies to be carried out before islets stored in this way will have functional properties similar to freshly isolated or cultured specimens Although so far only the culture technique has been employed on human islet tissue it seems plausible to assume that each of the storage systems may become of great importance in future attempts to transplant human islets

CONCLUSIONS AND SUMMARY

The quality of life for many juvenile diabetics is less than satisfactory Since there are reasons to believe that a more strict and physiological restoration of normoglycemia than that obtained with conventional insulin therapy might halt the progression of the vascular complications transplantation of the insulin producing cells has become a therapeutic alternative of great interest. Obviously whole organ pancreas transplants work beautifully as endocrine grafts but the increased complication risk due to the exocrine portion of the gland has at present slowed the progress in this field In experimental animals encouraging results have been obtained with implantation of isolated islets of Langerhans into rodents made diabetic by injections of B-cell cytotoxins The initial demonstrations of a normalization of the blood glucose homeostasis of the diabetic recipient has recently been found to be followed by the reversal or prevention of the diabetic vascular lesions Application of this technique to the human diabetic patient however requires that further experimental work must be done The yield of human pancreatic islet isolation will have to be increased or an alternative source for human islet tissue must become available Furthermore the immunological problems have to be successfully tackled Nevertheless trials of endocrine pancreas transplantation will take place during the forthcoming years on patients who are

already subjected to the risks of immunosuppressive treatment due to a kidney transplant. In case of even a limited success it might be of significant benefit for the diabetic patient crippled by long-term complications.

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Department of Histology
University of Uppsala
Box 571
S-751 23 Uppsala
Sweden

DISCUSSION

Sven-Erik Fagerberg It sounds fascinating that even established vascular complications could regress after islet transplantation. Did the basal membrane decrease in thickness or did depositions in the capillary wall disappear?

Arne Andersson The slide I showed was taken from Dr Federlin s recent publication He found that 4 months after the transplantation of 600 islets there was a normalization of the capillaries in the glomeruli and a nearly normal mesangium with only traces of PAS positive material

Hans Arnqvist If transplantation of pancreatic islets will be possible in the future the availability of transplants will be a problem. I therefore wonder if beta cells could undergo mitosis under *in vitro* conditions?

Arne Andersson. It appears quite likely that there will be a shortage of adult donor material One way to avoid this is to use fetal tissue It is of great interest in this context that Dr Hegre and collaborators in Minneapolis have shown that the endocrine cells of the fetal pancreas may regenerate so that there is a 25-fold increase in a few months after implantation under the kidney capsule of diabetic recipients

Anders Häger What progress had been made with the millipore chamber to avoid rejection of the transplanted beta cells?

Arne Andersson We tried to use this kind of equipment for transplantation a few years ago However we found that there was a tremendous fibroblast overgrowth within a few weeks when small millipore chambers were implanted intraperitoneally in diabetic mice I am quite sure that other laboratories have had the same experience

Yngve Larsson Would you like to comment Dr Andersson on the possible usefulness of fetal islet tissue as a source for transplantation to diabetic subjects

Arne Andersson As I just showed you long term reversal of chemically induced diabetes in experimental animals has been accomplished by transplantation of both fetal and neonatal pancreatic tissue The great advantage with this kind of transplant may be its great growth potential which thus means that less donor material should be needed. Whether this immature material in terms of glucose regulated insulin secretion will mature after the transplantation, however still remains an open question